PALM INTRANET

Day : Thursday
Date: 6/ 1/2000
Time: 13:07:00

Inventor Information for 08/487550

Inventor Name	City	State/Country
ANDERSON,DARRELL R.	ESCONDIDO	CALIFORNIA
BRAMS,PETER	SAN DIEGO	CALIFORNIA
HANNA,NABIL	OLIVENHAIN	CALIFORNIA
SHESTOWSKY,WILLIAM S.	SAN DIEGO	CALIFORNIA
HEARD,CHERYL	ENCINITAS	CALIFORNIA

Serial Info | Contents | Attorney/Agent Info | Continuity Data | Foreign Data | **Inventor**

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PALM INTRANET

Day : Thursday
Date: 6/ 1/2000
Time: 13:07:25

Inventor Information for 08/746361

Inventor Name	City	State/Country
ANDERSON,DARRELL R.	ESCONDIDO	CALIFORNIA
HANNA,NABIL	OLIVENHAIN	CALIFORNIA
BRAMS,PETER	SAN DIEGO	CALIFORNIA
HEARD,CHERYL	ENCINITAS	CALIFORNIA

Serial Info | Contents | Attorney/Agent Info | Continuity Data | Foreign Data | **Inventor**

Search Another: Serial# [ ] Search **or Patent#** [ ] Search

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t  Items  Description
      ---  -----  -----------
? b 410

>>>'IALOG' not recognized as set or accession number
? set hi ;set hi

       31may00 16:17:57 User208760 Session D1581.1
            $0.41    0.118 DialUnits File1
     $0.41  Estimated cost File1
     $0.05  TYMNET
     $0.46  Estimated cost this search
     $0.46  Estimated total session cost   0.118 DialUnits

File 410:Chronolog(R)  1981-2000 Mar/Apr
       (c) 2000 The Dialog Corporation plc

      Set  Items  Description
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?
HILIGHT set on as ''
HILIGHT set on as ''
? begin 652,653,654

       31may00 16:18:09 User208760 Session D1581.2
            $0.00    0.056 DialUnits File410
     $0.00  Estimated cost File410
     $0.01  TYMNET
     $0.01  Estimated cost this search
     $0.47  Estimated total session cost   0.174 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File 652:US Patents Fulltext  1971-1979
        (c) format only 2000 The Dialog Corp.
*File 652: Reassignment data current through 12/06/1999 recordings.
Due to recent processing problems, the SORT command is not working.
  File 653:US Patents Fulltext  1980-1989
        (c) format only 2000 The Dialog Corp.
*File 653: Reassignment data current through 12/06/1999 recordings.
Due to recent processing problems, the SORT command is not working.
  File 654:US Pat.Full.  1990-2000/May 30
        (c) format only 2000 The Dialog Corp.
*File 654: Reassignment data current through 12/06/1999 recordings.
Due to recent processing problems, the SORT command is not working.

      Set  Items  Description
      ---  -----  -----------
? s (16C10 or 7C10 or 20C9)(30n)(antibod? or hybridoma?)

             5  16C10
            10  7C10
             3  20C9
         42407  ANTIBOD?
          9459  HYBRIDOMA?
      S1     5  (16C10 OR 7C10 OR 20C9)(30N)(ANTIBOD? OR HYBRIDOMA?)
? t s1/3/all


 1/3/1     (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.
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03081954
Utility
PROTEIN D--AN IGD-BINDING PROTEIN OFHAEMOPHILUS INFLUENZAE

PATENT NO.: 6,025,484
ISSUED: February 15, 2000 (20000215)
INVENTOR(s): Forsgren, Arne, Sothonsvagen 4 B, S-230 11 Falsterbo, SE (Sweden)
[Assignee Code(s): 68000]
APPL. NO.: 8-969,761
FILED: November 13, 1997 (19971113)
PRIORITY: 9001949, SE (Sweden), May 31, 1990 (19900531)

This application is a continuation of application Ser. No. 08-798,026, filed on Feb. 6, 1997, now abandoned which is a continuation of application Ser. No. 08-469,011, filed on Jun. 5, 1995, now abandoned which is a divisional of application Ser. No. 07-946,499, filed on Nov. 9, 1992, now abandoned which is a 371 of PCT-SE91-00129, filed on Feb. 21, 1991.

FULL TEXT: 907 lines

1/3/2 (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) format only 2000 The Dialog Corp. All rts. reserv.

03042371
Utility
PROTEIN D-AN IGD BINDING PROTEIN OF HAEMOPHILUS INFLUENZAE

PATENT NO.: 5,989,828
ISSUED: November 23, 1999 (19991123)
INVENTOR(s): Forsgren, Arne, Sothonsvagen 4 B, S-230 11 Falsterbo, SE (Sweden)
[Assignee Code(s): 68000]
APPL. NO.: 8-747,381
FILED: November 12, 1996 (19961112)
PRIORITY: 9001949, SE (Sweden), May 31, 1990 (19900531)

This application is a continuation of application Ser. No. 08-465,307 filed Jun. 5, 1995 now abandoned, which is a divisional of application Ser. No. 07-946,499 now abandoned, filed Nov. 9, 1992, which corresponds to PCT-SE91-00129, filed Feb. 21, 1991.

FULL TEXT: 880 lines

1/3/3 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) format only 2000 The Dialog Corp. All rts. reserv.

02997532
Utility
VACCINE FOR MORAXELLA CATARRHALIS

PATENT NO.: 5,948,412
ISSUED: September 07, 1999 (19990907)
INVENTOR(s): Murphy, Timothy F., East Amherst, NY (New York), US (United States of America)
ASSIGNEE(s): The Research Foundation of State University of New York, (A U.S. Company or Corporation), Amherst, NY (New York), US (United States of America)
[Assignee Code(s): 5711]
APPL. NO.: 8-810,655

FILED: March 03, 1997 (19970303)

This application is a continuation-in-part of my earlier co-pending application U.S. Ser. No. 08-245,758, filed May 17, 1994, U.S. Pat. No. 5,607,846, which is incorporated herein by reference.

This invention was made with government support under grant A128304 awarded by the National Institutes of Health, and support by the Department of Veteran Affairs. The government has certain rights in the invention.

FULL TEXT: 1543 lines

1/3/4 (Item 4 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02931384
Utility
PROTEIN D-AN IGD-BINDING PROTEIN OF HAEMOPHILUS INFLUENZAE

PATENT NO.: 5,888,517
ISSUED: March 30, 1999 (19990330)
INVENTOR(s): Forsgren, Arne, Sothonsvagen 4 B, S-230 11 Falsterbo, SE (Sweden)
[Assignee Code(s): 68000]
APPL. NO.: 8-936,912
FILED: September 25, 1997 (19970925)
PRIORITY: 9001949, SE (Sweden), May 31, 1990 (19900531)
PCT-SE91-00129, WO (World Intellectual Property Org), February 21, 1991 (19910221)

This application is a continuation of application Ser. No. 08-468,618, filed Jun. 6, 1995, now abandoned; which is a continuation of Ser. No. 07-946,499, filed Nov. 9, 1992, now abandoned; which corresponds to PCT-SE91-00129, filed Feb. 21, 1991.

FULL TEXT: 853 lines

1/3/5 (Item 5 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02898478
Utility
PROTEIN D--AN IGD-BINDING PROTEIN OF HAEMOPHILUS INFLUENZAE
[Detection of bacteria by binding of nucleic acid probe or primer to sample DNA; bacterial meningitis, otitis media, sinusitis, pneumonia]

PATENT NO.: 5,858,677
ISSUED: January 12, 1999 (19990112)
INVENTOR(s): Forsgren, Arne, Sothonsvagen 4 B, S-230 11, Falsterbo, SE (Sweden)
[Assignee Code(s): 68000]
APPL. NO.: 8-968,885
FILED: November 05, 1997 (19971105)
PRIORITY: 9001949, SE (Sweden), May 31, 1990 (19900531)

This application is a continuation of application Ser. No. 08-798,025, filed Feb. 6, 1997 now abandoned, which is a continuation of Ser. No. 08-464,091, filed Jun. 5, 1995 now abandoned, which is a division of Ser. No. 07-946,499, filed Nov. 9, 1992 now abandoned, which corresponds to PCT-SE91-00129, filed Feb. 21, 1991 published as WO91-18926 Dec. 12, 1991.
FULL TEXT: 825 lines

? t s1/k/all

1/K/1 (Item 1 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... napthol and hydrogen peroxide. Protein D was also identified using-anti-protein D mouse monoclonal **antibodies 16C10**, 20G6 and 19B4 at 1:50 dilution in 1% OA-TBS. Protein 1 and 2...weight of 42,000 (42 kilodaltons). IgD and also all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) bound to the same band after electrophoresis of all extracts and subsequent...were tested by Western blot analysis with IgD and the three anti-protein D monoclonal **antibodies** (MAbs **16C10**, 20G6, 19B4).

Of all twelve species tested, only H. haemolyticus (5/5 strains) and H90 kilodaltons) with MAb **16C10** in all three strains. In an extract of one of the strains, a single 42 kilodaltons band was detected with the two other monoclonal **antibodies**. Two strains of H. ducreyi, H. parasuis (2 strains), H. parahaemolyticus (2 strains), H. sengius...electroblotted to an Immobilon filter. A protein that binds all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) and radiolabeled IgD could be detected in all three fractions (lane 2...

1/K/2 (Item 2 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... napthol and hydrogen peroxide. Protein D was also identified using anti-protein D mouse monoclonal **antibodies 16C10**, 20G6 and 19B4 at 1:50 dilution in 1% OA-TBS. Protein 1 and 2...weight of 42,000 (42 kilodaltons). IgD and also all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) bound to the same band after electrophoresis of all extracts and subsequent...were tested by Western blot analysis with IgD and the three anti-protein D monoclonal **antibodies** (MAbs **16C10**, 20G6, 19B4).

Of all twelve species tested, only H. haemolyticus (5/5 strains) and H90 kilodaltons) with MAb **16C10** in all three strains. In an extract of one of the strains, a single 42 kilodaltons band was detected with the two other monoclonal **antibodies**. Two strains of H. ducreyi, H. parasuis (2 strains), H. parahaemolyticus (2 strains), H. sengius...electroblotted to an Immobilon filter. A protein that binds all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) and radiolabeled IgD could be detected in all three fractions (lane 2...

1/K/3 (Item 3 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... day 67, and the fusion was performed on day 70 using standard methods. Two monoclonal **antibodies**, MAb 1C11 and MAb **7C10** , immunoreactive with the E protein were produced from this fusion.

A second fusion was performed...may be accomplished using methods known in the art for immunoaffinity chromatography. E-specific monoclonal **antibodies** , such as one or more of MAb 9G10, MAb 1B3, MAb 1C11, and MAb **7C10** , may be linked to a chromatographic matrix to form an affinity matrix. The outer membrane protein preparation is then incubated with the affinity matrix allowing the **antibodies** to bind to E . The affinity matrix is then washed to remove unbound components and...

1/K/4 (Item 4 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... electroblotted to an Immobilon filter. A protein that binds all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) and radiolabeled IgD could be detected in all three fractions (lane 2...

1/K/5 (Item 5 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... napthol and hydrogen peroxide. Protein D was also identified using anti-protein D mouse monoclonal **antibodies** **16C10**, 20G6 and 19B4 at 1:50 dilution in 1% OA-TBS. Protein 1 and 2...weight of 42,000 (42 kilodaltons). IgD and also all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) bound to the same band after electrophoresis of all extracts and subsequent...were tested by Western blot analysis with IgD and the three anti-protein D monoclonal **antibodies** (MAbs **16C10**, 20G6, 19B4).

Of all twelve species tested, only H. haemolyticus (5/5 strains) and H **16C10** in all three strains. In an extract of one of the strains, a single 42 kilodaltons band was detected with the two other monoclonal **antibodies** . Two strains of H. ducreyi, H. parasuis (2 strains), H. parahaemolyticus (2 strains), H. sengius...electroblotted to an Immobilon filter. A protein that binds all three anti-protein D monoclonal **antibodies** (**16C10**, 20G6 and 19B4) and radiolabeled IgD could be detected in all three fractions (lane 2...
? s (B7(w)1 or cd80)(30n)(antibod? or hybridoma?)

Processing
Processing
Processing
Processing
Processing
Processing
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Processing

```
          6698  B7
       2985589  1
           309  B7(W)1
            64  CD80
         42407  ANTIBOD?
          9459  HYBRIDOMA?
S2         82  (B7(W)1 OR CD80)(30N)(ANTIBOD? OR HYBRIDOMA?)
```

? s s2(40n)(ctla?)

```
            82  S2
           248  CTLA?
S3          28  S2(40N)(CTLA?)
```

? t s3/3/all

3/3/1 (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) format only 2000 The Dialog Corp. All rts. reserv.

03110269
Utility
BLOCKADE OF T LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING

PATENT NO.: 6,051,227
ISSUED: April 18, 2000 (20000418)
INVENTOR(s): Allison, James Patrick, Berkeley, CA (California), US (United States of America)
Leach, Dana R., Albany, CA (California), US (United States of America)
Krummel, Matthew F., Berkeley, CA (California), US (United States of America)

ASSIGNEE(s): The Regents of the University of California, Office of Technology Transfer, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-760,288
FILED: December 04, 1996 (19961204)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-646,605, filed May 8, 1996, now U.S. Pat. No. 5,811,097, which is a continuation-in-part of U.S. patent application Ser. No. 08-566,853, filed Dec. 4, 1995, now U.S. Pat. No. 5,855,887, which is a continuation-in-part of U.S. Ser. No. 08-506,666, filed Jul. 25, 1995, now abandoned.

This invention was made with government support under Contract Nos. CA 40041 and CA 09179 awarded by the National Institutes of Health. The Government has certain rights in this invention.

FULL TEXT: 1924 lines

3/3/2 (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03107586

Utility
HUMAN T CELL REACTIVE FELINE PROTEIN (TRFP) ISOLATED FROM HOUSE DUST AND USES THEREFOR

PATENT NO.: 6,048,962
ISSUED: April 11, 2000 (20000411)
INVENTOR(s): Gefter, Malcolm L., Lincoln, MA (Massachusettes), US (United States of America)
Garman, Richard D., Arlington, MA (Massachusettes), US (United States of America)
Greenstein, Julia L., West Newton, MA (Massachusettes), US (United States of America)
Kuo, Mei-chang, Winchester, MA (Massachusettes), US (United States of America)
Rogers, Bruce L., Belmont, MA (Massachusettes), US (United States of America)
Griffith, Irwin J., North Reading, MA (Massachusettes), US (United States of America)
Morgenstern, Jay P., Boston, MA (Massachusettes), US (United States of America)
Brauer, Andrew W., Salem, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Immulogic Pharmaceutical Corporation, (A U.S. Company or Corporation), Waltham, MA (Massachusettes), US (United States of America)
APPL. NO.: 8-430,014
FILED: April 27, 1995 (19950427)

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 08-300,928 filed Sep. 2, 1994, which is a continuation-in-part of U.S. patent application Ser. No. 07-807,529, filed Dec. 13, 1991 U.S. Pat. No. 5,547,669. This application is also a continuation-in-part of U.S. Ser. No. 08-006,116 filed Jan. 15, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-884,718, filed May 15, 1992, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-857,311, filed Mar. 25, 1992, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-662,276, filed Feb. 28, 1991, now abandoned, which is a

continuation-in-part of U.S. Ser. No. 07-431,565, filed Nov. 3, 1989, now abandoned. The contents of the above applications are incorporated herein by reference.

FULL TEXT: 5293 lines

3/3/3 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03104388
Utility
UNIQUE DENDRITIC CELL-ASSOCIATED C-TYPE LECTINS, DECTIN-1 AND DECTIN-2; COMPOSITIONS AND USES THEREOF

PATENT NO.: 6,046,158
ISSUED: April 04, 2000 (20000404)
INVENTOR(s): Ariizumi, Kiyoshi, Dallas, TX (Texas), US (United States of America)
Takashima, Akira, Irving, TX (Texas), US (United States of America)
ASSIGNEE(s): Board of Regents The University of Texas Systems, (A U.S. Company or Corporation), Austin, TX (Texas), US (United States of America)
[Assignee Code(s): 83960]
APPL. NO.: 8-772,440
FILED: December 20, 1996 (19961220)

The government owns rights in the present invention pursuant to grant number R01AR35068 and R01AR41150 from the National Institutes of Health.
FULL TEXT: 6726 lines

3/3/4 (Item 4 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03081633
Utility
HUMAN T CELL REACTIVE FELINE PROTEIN (TRFP) ISOLATED FROM HOUSE DUST AND USES THEREFOR

PATENT NO.: 6,025,162
ISSUED: February 15, 2000 (20000215)
INVENTOR(s): Rogers, Bruce L., Belmont, MA (Massachusettes), US (United States of America)
Griffith, Irwin J., North Reading, MA (Massachusettes), US (United States of America)
Morgenstern, Jay P., Boston, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Immulogic Pharmaceutical Corporation, (A U.S. Company or Corporation), Waltham, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 33875]
APPL. NO.: 8-430,944
FILED: April 28, 1995 (19950428)

RELATED APPLICATIONS

This application is a divisional of U.S. Ser. No. 08-300,928 (now allowed), filed Sep. 2, 1994, which is a continuation-in-part of U.S. patent application Ser. No. 07-807,529, filed Dec. 13, 1991 now U.S. Pat. No. 5,547,669, and also a continuation-in-part of U.S. Ser. No. 08-006,116 filed Jan. 15, 1993, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-884,718, filed May 15, 1992, now abandoned, which is a

continuation-in-part of U.S. Ser. No. 07-857,311, filed Mar. 25, 1992, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-662,276, filed Feb. 28, 1991, now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-431,565, filed Nov. 3, 1989, now abandoned. The contents of the above applications are incorporated herein by reference.

FULL TEXT: 5508 lines

3/3/5 (Item 5 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03075820
Utility
PEPTIDES OF HUMAN T CELL REACTIVE FELINE PROTEIN (TRFP)

PATENT NO.: 6,019,972
ISSUED: February 01, 2000 (20000201)
INVENTOR(s): Gefter, Malcolm L., Lincoln, MA (Massachusettes), US (United States of America)
Garman, Richard D., Arlington, MA (Massachusettes), US (United States of America)
Greenstein, Julia L., West Newton, MA (Massachusettes), US (United States of America)
Kuo, Mei-chang, Palo Alto, CA (California), US (United States of America)
Morville, Malcolm, Shrewsbury, MA (Massachusettes), US (United States of America)
Briner, Thomas J., Arlington, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): ImmuLogic Pharmaceutical Corporation, (A U.S. Company or Corporation), Waltham, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 33875]
APPL. NO.: 8-300,928
FILED: September 02, 1994 (19940902)

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 07-807,529, filed Dec. 13, 1991 now issued as U.S. Pat. No. 5,547,669. This application is also a continuation-in-part of U.S. Ser. No. 08-006,116 filed Jan. 15, 1993 now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-884,718, filed May 15, 1992 now abandoned, which is a continuation-in-part of U.S. Ser. No. 07-857,311, filed Mar. 25, 1992 now abandoned, which is a continuation-in part of U.S. Ser. No. 07-807,529, filed Dec. 13, 1991, now issued as U.S. Pat. No. 5,547,669 which is a continuation-in-part of U.S. Ser. No. 07-662,276, filed Feb. 28, 1991 now abandoned, and which is a continuation-in-part of U.S. Ser. No. 07-431,565, filed Nov. 3, 1989, now abandoned. The contents of the above applications are incorporated herein by reference.

FULL TEXT: 5247 lines

3/3/6 (Item 6 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03058421
Utility
METHODS FOR REGULATING GENE EXPRESSION

PATENT NO.: 6,004,941
ISSUED: December 21, 1999 (19991221)

INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
Gossen, Manfred, El Cerrito, CA (California), US (United States of America)
ASSIGNEE(s): BASF Aktiengesellschaft, (A Non-U.S. Company or Corporation), DE (Germany)
BASF Bioresearch Corporation, (A U.S. Company or Corporation), Worcester, MA (Massachusetts), US (United States of America)
Knoll Aktiengelellschaft, (A Non-U.S. Company or Corporation), DE (Germany)
[Assignee Code(s): 7016]
APPL. NO.: 8-485,740
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-383,754, filed Feb. 3, 1995, now U.S. Pat. No. 5,789,156. This application is also a continuation-in-part of U.S. Ser. No. 08-275,876, filed Jul. 15, 1994 now U.S. Pat. No. 5,654,168, which is a continuation-in-part of U.S. Ser. No. 08-270,637, filed Jul. 1, 1994, now abandoned. This application is also a continution-in-part of U.S. Ser. No. 08-260,452, filed Jun. 14, 1994 now U.S. Pat. No. 5,650,298, which is a continuation-in-part of U.S. Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned. This application is also a continution-in-part of U.S. Ser. No. 08-076,726, filed Jun. 14, 1993 now U.S. Pat. No. 5,464,758. The entire contents of each of these applications are incorporated herein by reference.

FULL TEXT: 4642 lines

3/3/7 (Item 7 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03042652
Utility
HETEROCYCLO-SUBSTITUTED IMIDAZOPYRAZINE PROTEIN TYROSINE KINASE INHIBITORS

PATENT NO.: 5,990,109
ISSUED: November 23, 1999 (19991123)
INVENTOR(s): Chen, Ping, Lawrenceville, NJ (New Jersey), US (United States of America)
Norris, Derek J., Trenton, NJ (New Jersey), US (United States of America)
Barrish, Joel C., Holland, PA (Pennsylvania), US (United States of America)
Iwanowicz, Edwin J., Cranbury, NJ (New Jersey), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Co , (A U.S. Company or Corporation), New York, NY (New York), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 9-262,525
FILED: March 04, 1999 (19990304)

This application claims priority from provisional U.S. application Ser. No. 60-076,789, filed Mar. 4, 1998, which is incorporated herein by reference in its entirety.

FULL TEXT: 2920 lines

3/3/8 (Item 8 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03028906
Utility

CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,977,318
ISSUED: November 02, 1999 (19991102)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America) [Assignee Code(s): 22921]
APPL. NO.: 8-488,062
FILED: June 07, 1995 (19950607)

This application is a divisional application of U.S. Ser. No. 08-375,390, filed Jan. 18, 1995, now U.S. Pat. No. 5,844,095, issued Dec. 1, 1981 which was a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, now U.S. Pat. No. 5,770,297, issued Jun. 23, 1998, which was a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3295 lines

3/3/9 (Item 9 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03019584
Utility
T CELL EPITOPES OF THE MAJOR ALLERGENS FROM DERMATOPHAGOIDES (HOUSE DUST MITE)

PATENT NO.: 5,968,526
ISSUED: October 19, 1999 (19991019)
INVENTOR(s): Garman, Richard D., Arlington, MA (Massachusettes), US (United States of America)
Greenstein, Julia L., West Newton, MA (Massachusettes), US (United States of America)
Kuo, Mei-chang, Winchester, MA (Massachusettes), US (United States of America)
Rogers, Bruce L., Belmont, MA (Massachusettes), US (United States of America)
Franzen, Henry M., Watertown, MA (Massachusettes), US (United States of America)
Chen, Xian, North Chelmsford, MA (Massachusettes), US (United States of America)
Evans, Sean, Acton, MA (Massachusettes), US (United States of America)
Shaked, Ze'ev, Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): Immulogic Pharamaceutical Corporation, (A U.S. Company or Corporation), Waltham, MA (Massachusetts), US (United States of America)
APPL. NO.: 8-478,572
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a divisional of U.S. Ser. No. 08-445,307, filed May 19, 1995, which is continuation-in-part of U.S. Ser. No. 08-227,772 filed Apr. 14, 1994. This application also claims priority to PCT-US95-04481 filed Apr. 12, 1995. All of the above identified cases are hereby incorporated herein by reference.

FULL TEXT: 7186 lines

3/3/10 (Item 10 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03019569
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,968,510
ISSUED: October 19, 1999 (19991019)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America) [Assignee Code(s): 22921]
APPL. NO.: 8-725,776
FILED: October 04, 1996 (19961004)

This application is a divisional application of U.S. Ser. No. 08-465,078, filed Jun. 5, 1995, which is a divisional application of Ser No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Serial No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, now U.S. Pat. No. 5,770,197 which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3280 lines

3/3/11 (Item 11 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02991195
Utility
B7-2: A CTLA4/CD28 LIGAND

PATENT NO.: 5,942,607
ISSUED: August 24, 1999 (19990824)
INVENTOR(s): Freeman, Gordon J., Brookline, MA (Massachusettes), US (United States of America)
Nadler, Lee M., Newton, MA (Massachusettes), US (United States of America)
Gray, Gary S., Brookline, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Dana-Farber Cancer Institute, (A U.S. Company or Corporation), Boston, MA (Massachusetts), US (United States of America)

[Assignee Code(s): 11804]
APPL. NO.: 8-101,624
FILED: July 26, 1993 (19930726)

GOVERNMENT FUNDING

This invention was made with government support under CA-40216-08 awarded by the National Institutes of Health. The U.S. government therefore has certain rights in this invention.

FULL TEXT: 2677 lines

3/3/12 (Item 12 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02958870
Utility
MICE TRANSGENIC FOR A TETRACYCLINE-INDUCIBLE TRANSCRIPTIONAL ACTIVATOR

PATENT NO.: 5,912,411
ISSUED: June 15, 1999 (19990615)
INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
Gossen, Manfred, El Cerrito, CA (California), US (United States of America)
ASSIGNEE(s): University of Heidelberg, (A Non-U.S. Company or Corporation), Heidelberg, DE (Germany)
[Assignee Code(s): 49705]
APPL. NO.: 8-487,472
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-383,754, filed Feb. 3, 1995, still pending. This application is also a continuation-in-part of U.S. Ser. No. 08-275,876, filed Jul. 15, 1994, now U.S. Pat. No. 5,654,168, which is a continuation-in-part of U.S. Ser. No. 08-270,637, filed Jul. 1, 1994, now abandoned. This application is also a continuation-in-part of U.S. Ser. No. 08-260,452, filed Jun. 14, 1994, now U.S. Pat. No. 5,650,298, which is a continuation-in-part of U.S. Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned. This application is also a continuation-in-part of U.S. Ser. No. 08-076,726, filed Jun. 14, 1993, now U.S. Pat. No. 5,464,758. The entire contents of each of these applications are incorporated herein by reference.

FULL TEXT: 4874 lines

3/3/13 (Item 13 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02931839
Utility
METHODS FOR REGULATING GENE EXPRESSION

PATENT NO.: 5,888,981
ISSUED: March 30, 1999 (19990330)
INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
Gossen, Manfred, El Cerrito, CA (California), US (United States of America)
Salfeld, Jochen G., North Grafton, MA (Massachusettes), US (United States of America)
Voss, Jeffrey W., West Boylston, MA (Massachusettes), US (United States of America)

ASSIGNEE(s): BASF Aktiengesellschaft, (A Non-U.S. Company or Corporation), Ludwigshafen, DE (Germany)
Knoll Aktiengesellschaft, (A Non-U.S. Company or Corporation), Ludwigshafen, DE (Germany)
[Assignee Code(s): 4911; 7016]
APPL. NO.: 8-479,306
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 08-260,452, U.S. Pat. No. 5,650,298, filed Jun. 14, 1994, which is a continuation-in-part of application Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned, the entire contents of each of which are incorporated herein by reference.

FULL TEXT: 3157 lines

3/3/14 (Item 14 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02928359
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,885,796
ISSUED: March 23, 1999 (19990323)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-465,078
FILED: June 05, 1995 (19950605)

This application is a divisional of U.S. Ser. No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, which is a continuation-in-part of U.S. Ser. No. 723,617 filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3215 lines

3/3/15 (Item 15 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02928151
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,885,579
ISSUED: March 23, 1999 (19990323)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)

Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Briston-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-889,666
FILED: July 08, 1997 (19970708)

This application is a divisional of U.S. Ser. No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, now U.S. Pat. No. 5,770,137, which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3241 lines

3/3/16 (Item 16 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02925563
Utility
CD9 ANTIGEN PEPTIDES AND ANTIBODIES THERETO

PATENT NO.: 5,883,223
ISSUED: March 16, 1999 (19990316)
INVENTOR(s): Gray, Gary S., 32 Milton Rd., Brookline, MA (Massachusettes), US (United States of America), 02146
[Assignee Code(s): 68000]
APPL. NO.: 8-453,925
FILED: May 30, 1995 (19950530)

RELATED APPLICATIONS

This application is a divisional application of Ser. No. 08-253,751 filed on Jun. 3, 1994, U.S. Pat. No. 5,858,358, which in turn is a continuation-in-part application of the following U.S. applications: U.S. Ser. No. 08-073,223 now abandoned, filed Jun. 4, 1993, entitled "Methods for Selectively Stimulating Proliferation of T cells"; U.S. Ser. No. 08-200,247, filed Feb. 23, 1994 which is a file wrapper continuation application of U.S. Ser. No. 864,805, filed Apr. 7, 1992, now abandoned, entitled "CD28 Pathway Immunoregulation"; U.S. Ser. No. 08-247,505, filed May 23, 1994 which is a file wrapper continuation application of U.S. Ser. No. 864,866, filed Apr. 7, 1992, now abandoned, entitled "Enhancement of CD28-Related Immune Response"; and U.S. Ser. No. 08-218,155, filed Mar. 25, 1994 which is a file wrapper continuation application of U.S. Ser. No. 864,807, filed Apr. 7, 1992, now abandoned, entitled "Immunotherapy Involving Stimulation of T sub h CD28 Lymphokine Production". Each of these applications is a continuation-in-part of U.S. Ser. No. 07-902,467, filed Jun. 19, 1992 which is a file wrapper continuation application of U.S. Ser. No. 275,433, filed Nov. 23, 1988, now abandoned, entitled "Immunotherapy Involving CD28 Stimulation", which corresponds to International Application Ser. No. PCT-US89-05304 (Publication No. WO 90-05541) filed Nov. 22, 1989. The contents of all of the aforementioned applications are hereby incorporated by reference.

FULL TEXT: 2014 lines

3/3/17 (Item 17 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02907545
Utility
ANIMALS TRANSGENIC FOR A TETRACYCLINE-REGULATED TRANSCRIPTIONAL INHIBITOR

PATENT NO.: 5,866,755
ISSUED: February 02, 1999 (19990202)
INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
Gossen, Manfred, El Cerrito, CA (California), US (United States of America)
ASSIGNEE(s): BASF Aktiengellschaft, (A Non-U.S. Company or Corporation), DE (Germany)
Knoll Aktiengellschaft, (A Non-U.S. Company or Corporation), DE (Germany)
[Assignee Code(s): 4911; 7016]
APPL. NO.: 8-486,814
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-383,754, filed Feb. 3, 1995, U.S. Pat. No. 5,789,156. This application is also a continuation-in-part of U.S. Ser. No. 08-275,876, filed Jul. 15, 1994, U.S. Pat No. 5,654,168, which is a continuation-in-part of U.S. Ser. No. 08-270,637, filed Jul. 1, 1994, now abandoned. This application is also a continution-in-part of U.S. Ser. No. 08-260,452, filed Jun. 14, 1994, U.S. Pat. No. 5,650,298, which is a continuation-in-part of U.S. Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned. This application is also a continution-in-part of U.S. Ser. No. 08-076,726, filed Jun. 14, 1993, U.S. Pat. No. 5,464,758. The entire contents of each of these applications are incorporated herein by reference.

FULL TEXT: 4690 lines

3/3/18 (Item 18 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02899094
Utility
MICE TRANSGENIC FOR A TETRACYCLINE-CONTROLLED TRANSCRIPTIONAL ACTIVATOR

PATENT NO.: 5,859,310
ISSUED: January 12, 1999 (19990112)
INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
Gossen, Manfred, El Cerrito, CA (California), US (United States of America)
Salfeld, Jochen G., Noth Graton, MA (Massachusettes), US (United States of America)
Voss, Jeffrey W., West Boylson, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): BASF Aktiengesellschaft, (A Non-U.S. Company or Corporation), Heidelberg, DE (Germany)
[Assignee Code(s): 7016]
APPL. NO.: 8-481,970
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a continuation-in-part of application Ser. No. 08-260,452, filed Jun. 14, 1994, now U.S. Pat. No. 5,650,298, which is a continuation-in-part of application Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned, the entire contents of each of which are incorporated

herein by reference.

FULL TEXT: 3215 lines

3/3/19 (Item 19 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02898165
Utility
METHODS FOR SELECTIVELY STIMULATING PROLIFERATION OF T CELLS

PATENT NO.: 5,858,358
ISSUED: January 12, 1999 (19990112)
INVENTOR(s): June, Carl H., Rockville, MD (Maryland), US (United States of America)
Thompson, Craig B., Chicago, IL (Illinois), US (United States of America)
Nabel, Gary J., Ann Arbor, MI (Michigan), US (United States of America)
Gray, Gary S., Brookline, MA (Massachusettes), US (United States of America)
Rennert, Paul D., Holliston, MA (Massachusettes), US (United States of America)
Freeman, Gordon J., Brookline, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Dana-Farber Cancer Institute, (A U.S. Company or Corporation), Boston, MA (Massachusetts), US (United States of America)
The Regents of the University of Michigan, (A U.S. Company or Corporation), Ann Arbor, MI (Michigan), US (United States of America)
The United States of America as represented by the Secretary of the Navy, (A U.S. Government Agency), Washington, DC (District of Columbia, US (United States of America)
[Assignee Code(s): 11804; 55176; 86584]
APPL. NO.: 8-253,751
FILED: June 03, 1994 (19940603)

RELATED APPLICATIONS

This application is a continuation-in-part of the following U.S. applications: U.S. Ser. No. 08-073,223, filed Jun. 4, 1993, now abandoned, entitled "Methods for Selectively Stimulating Proliferation of T cells"; U.S. Ser. No. 08-200,947, filed Feb. 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 07-864,805, filed Apr. 7, 1992, now abandoned, entitled "CD28 Pathway Immunoregulation"; U.S. Ser. No. 08-247,505, filed May 23, 1994, now abandoned, which is a continuation of U.S. Ser. No. 07-864,866, filed Apr. 7, 1992, now abandoned, entitled "Enhancement of CD28-Related Immune Response"; and U.S. Ser. No. 08-218,155, filed Mar. 25, 1994, now abandoned, which is a continuation of U.S. Ser. No. 07-864,807, filed Apr. 7, 1992, now abandoned, entitled "Immunotherapy Involving Stimulation of T sub h CD28 Lymphokine Production". Each of these applications is a continuation-in-part of U.S. Ser. No. 07-902,467, filed June 16, 1992, now abandoned, which is a continuation of U.S. Ser. No. 07-275,433, filed Nov. 23, 1988, now abandoned, entitled "Immunotherapy Involving CD28 Stimulation", which corresponds to International Application Ser. No. PCT-US89-05304 (Publication No. WO 90-05541) filed Nov. 22, 1989. The contents of each of these applications is incorporated herein by reference.

FULL TEXT: 2108 lines

3/3/20 (Item 20 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02895364
Utility
BLOCKADE OF LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING
[Lymphocyte activation in response to antigen]

PATENT NO.: 5,855,887
ISSUED: January 05, 1999 (19990105)
INVENTOR(s): Allison, James Patrick, Berkeley, CA (California), US (United States of America)
Leach, Dana R., Albany, CA (California), US (United States of America)
Krummel, Matthew F., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-566,853
FILED: December 04, 1995 (19951204)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08-506,666, filed Jul. 25, 1995, now abandoned.

This invention was made with government support under Contract Nos. CA 40041 and CA 09179 awarded by the National Institutes of Health. The Government has certain rights in this invention.

FULL TEXT: 1317 lines

3/3/21 (Item 21 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02890599
Utility
SOLUBLE CTLA4 MOLECULES AND USES THEREOF

PATENT NO.: 5,851,795
ISSUED: December 22, 1998 (19981222)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), New York, NY (New York), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-459,818
FILED: June 02, 1995 (19950602)

This is a division of application Ser. No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Ser. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which

are incorporated by reference into the present application.

FULL TEXT: 3260 lines

3/3/22 (Item 22 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02881963
Utility
CTLA4 IG FUSION PROTEINS

PATENT NO.: 5,844,095
ISSUED: December 01, 1998 (19981201)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), New York, NY (New York), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-375,390
FILED: January 18, 1995 (19950118)

This application is a continuation-in-part of U.S. Ser. No. 08-069,693, filed May 28, 1993, now abandoned, which is a continuation of U.S. Ser. No. 07-723,617, filed Jun. 27, 1991, now abandoned, and this application is also a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3204 lines

3/3/23 (Item 23 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02856714
Utility
T CELL EPITOPES OF THE MAJOR ALLERGENS FROM DERMATOPHAGOIDES (HOUSE DUST MITE)
[Therapeutic composition comprising mixture of specified isolated peptides]

PATENT NO.: 5,820,862
ISSUED: October 13, 1998 (19981013)
INVENTOR(s): Garman, Richard D., Arlington, MA (Massachusettes), US (United States of America)
Greenstein, Julia L., West Newton, MA (Massachusettes), US (United States of America)
Kuo, Mei-chang, Winchester, MA (Massachusettes), US (United States of America)
Rogers, Bruce L., Belmont, MA (Massachusettes), US (United States of America)
Franzen, Henry M., Watertown, MA (Massachusettes), US (United States of America)
Chen, Xian, North Chelmsford, MA (Massachusettes), US (United States of America)
Evans, Sean, Acton, MA (Massachusettes), US (United States of

America)
Shaked, Ze'ev, Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): Immulogic Pharmaceutical Corporation, (A U.S. Company or Corporation), Waltham, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 33875]
APPL. NO.: 8-482,142
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a divisional of U.S. Ser. No. 08-445,307, filed May 19, 1995 which is a continuation-in-part of U.S. Ser. No. 08-227,772 filed Apr. 14, 1994, now abandoned, which is a continuation-in-part of PCT-US93-03471 filed Apr. 14, 1993.

FULL TEXT: 6810 lines

3/3/24 (Item 24 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02850005
Utility
METHODS FOR REGULATING GENE EXPRESSION
[Tetracycline-responsive fusion proteins]

PATENT NO.: 5,814,618
ISSUED: September 29, 1998 (19980929)
INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
Gossen, Manfred, El Cerrito, CA (California), US (United States of America)
ASSIGNEE(s): BASF Aktiengesellschaft, (A Non-U.S. Company or Corporation), Ludwigshafen, DE (Germany)
Knoll Aktiengesellchaft, (A Non-U.S. Company or Corporation), Ludwigshafen, DE (Germany)
[Assignee Code(s): 4911; 7016]
APPL. NO.: 8-485,978
FILED: June 07, 1995 (19950607)

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-383,754, filed Feb. 3, 1995. This application is also a continuation-in-part of U.S. Ser. No. 08-275,876, U.S. Pat. No. 5,654,168, filed Jul. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-270,637, filed Jul. 1, 1994, now abandoned. This application is also a continuation-in-part of U.S. Ser. No. 08-260,452, U.S. Pat. No. 5,650,298, filed Jun. 14, 1994, which is a continuation-in-part of U.S. Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned. This application is also a continuation-in-part of U.S. Ser. No. 08-076,726, U.S. Pat. No. 5,464,758 filed Jun. 14, 1993. The entire contents of each of these applications are incorporated herein by reference.

FULL TEXT: 4705 lines

3/3/25 (Item 25 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02846287
Utility
BLOCKADE OF T LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING

[Decreasing growth of tumor cells by administering blocking agent which binds to extracellular domain of cytotoxic T-lymphocyte-associated molecule and inhibits signaling]

PATENT NO.: 5,811,097
ISSUED: September 22, 1998 (19980922)
INVENTOR(s): Allison, James Patrick, Berkeley, CA (California), US (United States of America)
Leach, Dana R., Albany, CA (California), US (United States of America)
Krummel, Matthew F., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-646,605
FILED: May 08, 1996 (19960508)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08-566,853, filed Dec. 4, 1995, which is a continuation-in-part of U.S. patent application Ser. No. 08-506,666, filed Jul. 25, 1995 now abandoned.

This invention was made with government support under Contract Nos. CA 40041 and CA 09179 awarded by the National Institutes of Health. The Government has certain rights in this invention.

FULL TEXT: 1738 lines

3/3/26 (Item 26 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02806273
Utility
MYPPPY VARIANTS OF CTL A4 AND USES THEREOF

PATENT NO.: 5,773,253
ISSUED: June 30, 1998 (19980630)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Peach, Robert, Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-505,058
FILED: July 21, 1995 (19950721)

This application is a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994 which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, the contents of which is incorporated by reference into the present application.

FULL TEXT: 1624 lines

3/3/27 (Item 27 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02778834
Utility
METHODS AND MATERIALS FOR THE INDUCTION OF T CELL ANERGY

PATENT NO.: 5,747,034
ISSUED: May 05, 1998 (19980505)
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APPL. NO.: 8-200,716
FILED: February 18, 1994 (19940218)

This application is a continuation-in-part of U.S. application Ser. No. 08-015,147, filed Feb. 3, 1993, now pending, which is a continuation-in-part of U.S. application Ser. No. 07-910,222, filed Jul. 9, 1992, U.S. Pat. No. 5,397,703.

FULL TEXT: 2036 lines

3/3/28 (Item 28 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02605652
Utility
TETRACYCLINE REGULATED TRANSCRIPTIONAL MODULATORS WITH ALTERED DNA BINDING SPECIFICITIES
[Fusion proteins, eukaryotic cells]

PATENT NO.: 5,589,362
ISSUED: December 31, 1996 (19961231)
INVENTOR(s): Bujard, Hermann, Heidelberg, DE (Germany)
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[Assignee Code(s): 4911; 7016]
APPL. NO.: 8-485,971
FILED: June 07, 1995 (19950607)
RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-383,754, filed Feb. 3, 1995. This application is also a continuation-in-part of U.S. Ser. No. 08-275,876, filed Jul. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-270,637, filed Jul. 1, 1994, now abandoned. This application is also a continuation-in-part of U.S. Ser. No. 08-260,452, filed Jun. 14, 1994, which is a continuation-in-part of U.S. Ser. No. 08-076,327, filed Jun. 14, 1993, now abandoned. This application is also a continuation-in-part of U.S. Ser. No. 08-076,726, filed Jun. 14, 1993, now U.S. Pat. No. 5,464,758. The entire contents of each of these applications are incorporated herein by reference.

FULL TEXT: 4664 lines
? t s3/k/all

3/K/11 (Item 11 from file: 654)

... graphic representation of the response of CD4+T cells to costimulation provided by either B7 (**B7-1**) transfected CHO cells (panel a) or syngeneic activated B lymphocytes (panel b) cultured in media, anti-CD3 alone, or anti-CD3 in the presence of the following monoclonal **antibodies** or recombinant proteins: alpha B7 (**B7-1**); **CTLA4** -Ig; Fab alpha CD28; or control Ig fusion protein (isotype control for **CTLA4Ig**); or alpha B5 (the isotype control for anti-B7). sup 3 H-Thymidine incorporation was...3B are a graphic representations of the response of CD4+T cell costimulation provided by **B7-1** positive (panel a) or **B7-1** negative (panel b) activated syngeneic B lymphocytes cultured in media, anti-CD3 alone, or anti-CD3 in the presence of the following monoclonal **antibodies** or recombinant proteins: alpha BB-1 (**B7-1** and B7-3); alpha B7 (**B7-1**); **CTLA4** -Ig; Fab alpha CD28; control Ig fusion protein or alpha B5. sup 3 H-Thymidine...

...experiments.

FIG. 4 is a graphic representation of the cell surface expression of the three **CTLA4Ig** binding proteins (B7-1, B7-2 and B7-3). These CTLA4/CD28 ligands can be expression after B cell activation and their reactivity with **CTLA4Ig** and anti-B7 monoclonal **antibodies**. **B7-1** (mAb 133), **B7-1** and B7-3 (mAb BB-1) and **B7-1**, B7-2 and B7-3 (**CTLA4Ig**) binding counter-receptors on fractionated **B7-1** positive and **B7-1** negative activated B lymphocytes. The results are representative of five experiments.

FIG. 5 is a graphic representations of temporal surface expression of B7-1 (**CTLA4Ig** and mAbs BB-1 and 133), B7-3 (**CTLA4** and mAb BB1) and B7-2 (**CTLA4**-Ig) counter-receptors on splenic B cells activated by sIg crosslinking. Following activation, cells were...in media, anti-CD3 alone, or anti-CD3 in the presence of the following monoclonal **antibodies** or recombinant protein: alpha B7(**B7-1**); (**CTLA4** -Ig; Fab alpha CD28; and alpha B5. sup 3 H-Thymidine incorporation was assessed for... by PMA and COS cells transfected with vector alone (vector), or with a vector expressing **B7-1** (**B7-1**) or B7-2 (B7-2). Inhibition studies were performed with the addition of either no **antibody** (no ...anti-B5 mAb (B5)(panel D), Fab fragment of anti-CD28 (CD28 Fab)(panel E), **CTLA4Ig** (**CTLA4** -Ig)(panel F), or Ig control protein (control Ig) (panel G) to the PMA stimulated...
... about 24 hours following stimulation with either anti-immunoglobulin or anti-MHC class II monoclonal **antibody** . The B7-2 antigen induces detectable IL-2 secretion and T cell proliferation. At about 48 to 72 hours post activation, B cells express both **B7-1** and a third **CTLA4** counter-receptor identified by a monoclonal **antibody** BB-1 (Yokochi, T., et al. (1982) J. Immunol. 128, 823-827), termed B7-3...g., DEAE-Dextran) and allowed to replicate and express the cDNA inserts. The transfectants expressing **B7-1** antigen are depleted with an anti-**B7-1** monoclonal **antibody** (e.g., 133 and B1.1) and anti-murine IgG and IgM coated immunomagnetic beads...

... B7-2 and B7-3 antigen were positively selected by reacting the fusion proteins with **CTLA4** -Ig and CD28-Ig followed by panning with anti-human ... B7 (panel a). Both proliferation and IL-2 secretion were

totally inhibited by blocking the **B7-1** molecule on CHO cells with either anti-**B7-1** monoclonal **antibody** or by a fusion protein for its high affinity receptor, **CTLA4** . Similarly, proliferation and IL-2 secretion were abrogated by blocking **B7-1** signalling via CD28 with Fab anti-CD28 monoclonal **antibody**. Control monoclonal **antibody** or control fusion protein had no effect. Nearly identical costimulation for proliferation and IL- ...by splenic B cells activated with anti-Ig for 72 hours (panel b). Though anti-**B7-1** monoclonal **antibody** could completely abrogate both proliferation and IL-2 secretion delivered by CHO-B7, anti-**B7-1** monoclonal **antibody** consistently inhibited proliferation induced by activated B cells by only 50% whereas IL-2 secretion was totally inhibited. In contrast to the partial blockage of proliferation induced by anti-**B7-1** monoclonal **antibody**, both **CTLA4**-Ig and Fab anti-CD28 monoclonal **antibody** completely blocked proliferation and IL-2 secretion. Identical results were obtained when the responding T...

...CTLA4 Ligand(s) Distinct from B7-1

In light of the above observations, whether other **CTLA4** binding counter-receptors were expressed on activated B cells was determined. To this end, human with anti-Ig and then stained with an anti-**B7-1** monoclonal **antibody** (B1.1) which does not inhibit **B7-1** mediated costimulation. B7+ and B7- fractions were isolated by flow cytometric cell sorting. The resulting...

... 4 (data not shown). As was observed with the unfractionated activated B cell population, anti-**B7-1** monoclonal **antibody** (133) inhibited proliferation only 50% but consistently abrogated IL-2 secretion. As above, **CTLA4** -Ig binding or blockade of CD28 with Fab anti-CD28 monoclonal **antibody** completely inhibited both proliferation and IL-2 secretion. Control monoclonal antibody and control-Ig were not inhibitory. In an attempt to identify other potential **CTLA4** /CD28 binding costimulatory ligand(s) which might account for the residual, non-B7 mediated proliferation... by detectable IL-2 (FIG. 3b) or IL-4 (data not shown) accumulation and anti-**B7-1** monoclonal **antibody** did not inhibit proliferation. However, **CTLA4** -Ig, Fab anti-CD28 monoclonal **antibody**, and BB-1 monoclonal **antibody** all completely inhibited proliferation.

Phenotypic analysis of the B7+ and B7- activated splenic B cells...

... functional results. As seen in FIG. 4, B7+ activated splenic B cells stained with anti-**B7-1** (133) monoclonal **antibody**, BB-1 monoclonal **antibody**, and bound **CTLA4** -1g. In contrast, B7- activated splenic B cells did not stain with anti-**B7-1** (133) monoclonal **antibody** but did stain with BB-1 monoclonal **antibody** and **CTLA4** -Ig. These phenotypic and functional results demonstrate that both B7+ and B7- activated (72 hours) human B lymphocytes express **CTLA4** binding counter- ... proliferate without detectable IL-2 secretion; and 2) are identified by the BB-1 monoclonal **antibody** but not anti-**B7-1** monoclonal **antibody**.

Example 3: Three Distinct **CTLA4**/CD28 Ligands Are Expressed Following Human B Cell Activation

To determine the sequential expression of **CTLA4** binding counter-receptors following activation, human splenic B cells were activated by crosslinking of either...sup 3 H-Thymidine incorporation). Neither proliferation nor IL-2 accumulation was inhibited by anti-**B7-1** (133) or BB-1. In contrast with **CTLA4**-Ig and Fab anti-CD28 monoclonal **antibody** totally abrogated proliferation and IL-2 accumulation. B cells activated for ...costimulation which resulted in nearly maximal proliferation and IL-2 secretion (FIG. 7b). Here, anti-**B7-1** (133) monoclonal **antibody**, inhibited proliferation approximately 50% but totally blocked IL-2 accumulation. BB-1 monoclonal

antibody totally inhibited both proliferation and IL-2 secretion. As above, **CTLA4**-Ig and Fab anti-CD28 also totally blocked proliferation and IL-2 production. Finally, 72...

...by MHC class II rather than Ig crosslinking. These results indicate that there are three **CTLA4** binding molecules that are temporarily expressed on activated B cells and each can induce submitogenically stimulated T cells to proliferate. Two of these molecules, the early **CTLA4** binding counter-receptor (B7-2) and **B7-1** (133) induce IL-2 production whereas B7-3 induces proliferation without detectable IL-2 production.

Previous studies provided conflicting evidence whether the anti-B7 monoclonal **antibody**, 133 and monoclonal **antibody** BB-1 identified the same molecule (Freedman, A. S. et al. (1987) ...which binds monoclonal antibody BB-1.

Our present findings confirm that there is an additional **CTLA4** counter-receptor identified by the BB-1 monoclonal **antibody**, B7-3, and that this protein appears to be functionally distinct from **B7-1** (133). Although the expression of **B7-1** and B7-3 following B cell activation appears to be concordant on B7 positive B...al J. Exp. Med. (accepted for publication)). These data indicate that the BB-1 monoclonal **antibody** recognizes an epitope on the **B7-1** protein and that this epitope is also found on a distinct B7-3 protein, which also has costimulatory function. Phenotypic and blocking studies demonstrate that the BB-1 monoclonal **antibody** could detect one (on B7 negative cells) or both (on B7 positive cells) of these proteins. In contrast, the anti-B7 monoclonal **antibodies**, 133 and B1.1 detect only the **B7-1** protein. Taken together, these results suggest that by 48 hours post B-cell activation by crosslinking of surface immunoglobulin or MHC class II, B cells express two distinct **CTLA4** binding counter-receptors, one identified by both anti-B7 and BB-1 monclonal antibodies and...

3/K/12 (Item 12 from file: 654)
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... immunosuppression can be used. Such agents may include inhibitors of costimulatory molecules (e.g., a **CTLA4Ig** fusion protein, soluble CD4, anti-CD4 **antibodies**, anti-**B7-1** and/or anti-B7-2 **antibodies** or anti-gp39 **antibodies**).

Finally, in certain situations, a delivery vehicle for cells expressing a therapeutic gene can be...

3/K/13 (Item 13 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... immunosuppression can be used. Such agents may include inhibitors of costimulatory molecules (e.g., a **CTLA4Ig** fusion protein, soluble CD4, anti-CD4 **antibodies**, anti-**B7-1** and/or anti-B7-2 **antibodies** or anti-gp39 **antibodies**).

Finally, in certain situations, a delivery vehicle for cells expressing a therapeutic gene can be...

3/K/14 (Item 14 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

...islet cells.

EXAMPLE 6

By site-specific and homolog mutagenesis, we have identified regions in **CTLA4Ig** which are required for its high avidity binding to **B7-1**. The following is a description of how to make soluble **CTLA4**/CD28 hybrid fusion proteins which bind B7.

MATERIALS AND METHODS

Monoclonal **antibodies** (mabs). Murine mAb's specific for **CTLA4** were prepared and characterized as previously described (Linsley et al. J. Ex. Med., (1992) 176:1595-1604). **Antibody** 9.3 (anti-CD28) has been described previously ((Hansen et al., Immunogenetics 10:247-260 (1980)).

Cell Culture. The preparation of stably transfected **B7-1** positive CHO cells has been previously described (Linsley et al., ... assays, the binding of the fusion proteins to a B cell line, B414, that expresses **B7-1** , was determined following incubation of the cells with either cell supernatants or purified fusion protein. Bound fusion protein was detected with an **antibody** to the C-terminus region of the fusion protein (FIGS. 28-31).

Specifically, in the ELISA and FACS assays, when detecting the binding of the **CTLA4**-E7 fusion protein, antibodies which recognize and bind the E7 portion of the fusion protein...were used (M. Kahn et al. J. Immunol. (1991) 146(9):3235-41).

The soluble **CTLA4** fusion protein/antibody complex was in turn visualized with a FITC-labelled second **antibody**. Binding of all the different fusion proteins to the B cells was competitively inhibited by soluble **CTLA4Ig**.

In the ELISA assays, **B7-1** (2.5 mu g/ml) was immobilized to 96 well microtiter plates, samples were blocked...

3/K/15 (Item 15 from file: 654)

...islet cells.

EXAMPLE 6

By site-specific and homolog mutagenesis, we have identified regions in **CTLA4Ig** which are required for its high avidity binding to **B7-1**. The following is a description of how to make soluble **CTLA4**/CD28 hybrid fusion proteins which bind B7.

MATERIALS AND METHODS

Monoclonal **antibodies** (mAbs)

Murine mAb's specific for **CTLA4** were prepared and characterized as previously described (Linsley et al. J. Ex. Med., (1992) 176:1595-1604). **Antibody** 9.3 (anti-CD2B) has been described previously ((Hansen et al. Immunogenetics 10:247-260 (1980)).

Cell Culture

The preparation of stably transfected **B7-1** positive CHO cells has been previously described (Linsley et al., in J. Exp. Med. 173... assays, the binding of the fusion proteins to a B cell line, B414, that expresses **B7-1** , was determined following incubation of the cells with either cell supernatants or purified fusion protein. Bound fusion protein was detected with an **antibody** to the C-terminus region of the fusion protein (FIGS. 28-31).

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The soluble **CTLA4** fusion protein/antibody complex was in turn visualized with a FITC-labelled second **antibody**. Binding of all the different fusion proteins to the B cells was competitively inhibited by soluble **CTLA4Ig**.

In the ELISA assays, **B7-1** (2.5 mu g/ml) was immobilized to 96 well microtiter plates, samples were blocked...

3/K/16 (Item 16 from file: 654)
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... weeks in culture. Cells were changed to fresh medium at each restimulation with anti-CD3 **antibody**. Stimulations were spaced at ten day intervals. The cells were restimulated whenever cell volume decreased to <400 fl.

In another experiment, cyclic expression of the **B7-1** antigen was used to determine the time for T cell restimulation. The cells obtained from the experiment shown in FIG. 10 were stained with a **CTLA**-4Ig fusion protein (obtained from Repligen Corporation; see also Linsley P. S. et al. (1991...

3/K/17 (Item 17 from file: 654)
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... specific immunosuppression can be used. Such agents may include inhibitorsof costimulatory molecules (e.g., a **CTLA41g** fusion protein, soluble CD4, anti-CD4 **antibodies**, anti-**B7-1** and/or anti-B7-2 **antibodies** or anti-gp39 **antibodies**).

Finally, in certain situations, a delivery vehicle for cells expressing a therapeutic gene can be...

3/K/18 (Item 18 from file: 654)
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... immunosuppression can be used. Such agents may include inhibitors of costimulatory molecules (e.g., a **CTLA4Ig** fusion protein, soluble CD4, anti-CD4 **antibodies**, anti-**B7-1** and/or anti-B7-2 **antibodies** or anti-gp39 **antibodies**)

Finally, in certain situations, a delivery vehicle for cells expressing a therapeutic gene can be...

3/K/19 (Item 19 from file: 654)
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... weeks in culture. Cells were changed to fresh medium at each restimulation with anti-CD3 **antibody**. Stimulations were spaced at ten day intervals. The cells were restimulated whenever cell volume decreased to <400 fl.

In another experiment, cyclic expression of the **B7-1** antigen was used to determine the time for T cell restimulation. The cells obtained from the experiment shown in FIG. 10 were stained with a **CTLA**-4Ig fusion protein (obtained from Repligen Corporation; see also Linsley P. S. et al. (1991...

3/K/20 (Item 20 from file: 654)
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...more usually about 10 sup - M, i.e. binding affinities normally observed with specific monoclonal **antibodies**.

A number of screening assays are available for blocking agents. The components of such assays will typically include **CTLA**-4 protein; and optionally a **CTLA**-4 activating agent, e.g. **CD80**, CD86, etc. The assay mixture will also comprise a candidate pharmacological agent. Generally a plurality...
...cells. Three of the mice remained tumor free beyond 80 days. It is clear that **CTLA** -4 blockade significantly enhanced rejection of the B7 negative tumor cells.
c) Injection of Mice with B7-51BLim10 Tumor Cells and Monoclonal **Antibodies**.

51BLim10 cells were transfected as described above, with a plasmid containing the gene for murine **B7-1**, and cloned by limiting dilution. The B7-51BLim10 tumor cells were harvested from tissue culture...

3/K/21 (Item 21 from file: 654)
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...islet cells.

EXAMPLE 6

By site-specific and homolog mutagenesis, we have identified regions in **CTLA4Ig** which are required for its high avidity binding to **B7-1**. The following is a description of how to make soluble **CTLA4** /CD28 hybrid fusion proteins which bind B7.

MATERIALS AND METHODS

Monoclonal **antibodies** (mAbs). Murine mAb's specific for **CTLA4** were prepared and characterized as previously described (Linsley et al. J. Ex. Med., (1992) 176:1595-1604). **Antibody** 9.3 (anti-CD28) has been described previously ((Hansen et al., Immunogenetics 10:247-260 (1980)).

Cell Culture

The preparation of stably transfected **B7-1** positive CHO ... assays, the binding of the fusion proteins to a B cell line, B414, that expresses **B7-1** , was determined following incubation of the cells with either cell supernatants or purified fusion protein. Bound fusion protein was detected with an **antibody** to the C-terminus region of the fusion protein (FIGS. 28-31).

Specifically, in the ELISA and FACS assays, when detecting the binding of the **CTLA4**-E7 fusion protein, antibodies which recognize and bind the E7 portion of the fusion protein...were used (M. Kahn et al. J. Immunol. (1991) 146(9):3235-41).

The soluble **CTLA4** fusion protein/antibody complex was in turn visualized with a FITC-labelled second **antibody**. Binding of all the different fusion proteins to the B cells was competitively inhibited by soluble **CTLA4Ig**.

In the ELISA assays, **B7-1** (2.5 mu g/ml) was immobilized to 96 well microtiter plates, samples were blocked...

3/K/22 (Item 22 from file: 654)
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...islet cells.

EXAMPLE 6

By site-specific and homolog mutagenesis, we have identified regions in **CTLA4Ig** which are required for its high avidity binding to **B7-1**. The following is a description of how to make soluble **CTLA4** /CD28 hybrid fusion proteins which bind B7.

MATERIALS AND METHODS

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Specifically, in the ELISA and FACS assays, when detecting the binding of the **CTLA4**-E7 fusion protein, antibodies which recognize and bind the E7 portion of the fusion protein...were used (M. Kahn et al. J. Immunol. (1991) 146(9): 3235-41).

The soluble **CTLA4** fusion protein/antibody complex was in turn visualized with a FITC-labelled second **antibody**. Binding of all the different fusion proteins to the B cells was competitively inhibited by soluble **CTLA4Ig**.

In the ELISA assays, **B7-1** (2.5 mu g/ml) was immobilized to 96 well microtiter plates, samples were blocked...

3/K/23 (Item 23 from file: 654)
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... T cell nonresponsiveness or reduced T cell responsiveness. In addition, there are a number of **antibodies** or other reagents capable of blocking the delivery of costimulatory signals such as the "second signal" which include, but are not limited to B7 (including **B7-1**, B7-2, and BB-1), CD28, **CTLA4**, CD40 CD40L CD54 and CD11 a/18 (Jenkins and Johnson, Current Opinion in Immunology, 5...

3/K/24 (Item 24 from file: 654)
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... immunosuppression can be used. Such agents may include inhibitors of costimulatory molecules (e.g., a **CTLA4Ig** fusion protein, soluble CD4, anti-CD4 **antibodies**, anti-**B7-1** and/or anti-B7-2 **antibodies** or anti-gp39 **antibodies**).

Finally, in certain situations, a delivery vehicle for cells expressing a therapeutic gene can be...

3/K/25 (Item 25 from file: 654)
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... usually about 10 sup -8 M, i.e. binding affinities normally observed with specific monoclonal **antibodies**.

A number of screening assays are available for blocking agents. The components of such assays will typically include **CTLA**-4 protein; and optionally a **CTLA**-4 activating agent, e.g. **CD80**, CD86, etc. The assay mixture will also comprise a candidate pharmacological agent. Generally a plurality...cells. Three of the mice remained tumor free beyond 80 days. It is clear that **CTLA**-4 blockade significantly enhanced rejection of the B7 negative tumor cells.

c) Injection of Mice with B7-51BLim10 Tumor Cells and Monoclonal **Antibodies** . 51BLim10 cells were transfected as described above, with a plasmid containing the gene for murine **B7-1**, and cloned by limiting dilution. The B7-51BLim10 tumor cells were harvested from tissue culture... concentrations. Where indicated, anti-CD28 was added at a 1:1000 dilution of ascites, anti-**B7-1** was added at 5 mu g/ml and anti-B7-2 was added at 20 mu g/ml, and equal quantities of non-specific control **antibody** 560.31 were added. For FAb experiments, anti-CD28, anti-**CTLA** -4 or control FAb fragments were added at 100 mu g/ml. Cultures were incubated...B7 molecules on cells in these cultures appear to supply costimulation, since addition of anti-**B7-1**/B7-2 **antibodies** significantly inhibited the response. Further, increased CD28 signaling via anti-CD28 **antibodies** enhanced the proliferative response. This increase may have been mediated by immobilization of **antibody** on FcR sup + B cells or by the formation of **antibody** microaggregates. Interestingly, the addition of anti-CD28 and anti-**B7-1** /B7-2 induced a slight but reproducible increase in proliferation compared to anti-CD28 by itself, suggesting that another B7 ligand besides CD28 (i.e. **CTLA** -4) might be important in downregulating the response of T cells to SEB.

To address... produced results identical to those obtained with animals treated with anti-CD28 alone.

B7/CD28/**CTLA** -4 Interactions Are Important for Regulating the SEB Response In Vitro. The data presented here...

... signals in the response of murine T cells to the superantigen SEB. Endogenous interactions of **B7-1**/B7-2 with CD28 are important for promoting proliferation since blocking with either anti-**B7-1**/2 **antibodies** or anti-CD28 FAb fragments drastically reduced SEB-induced proliferation. In contrast, engagement of CD28 by intact anti-CD28 **antibodies** increases proliferation above the threshold provided by APC. This increase is probably due to microaggregation ... aggregation of anti-CD28 antibodies leading to efficient crosslinking of CD28.

In contrast to CD28, **CTLA**-4 interactions with B7 molecules dampens the T cell response to SEB. The observation that anti-**CTLA**-4 FAb fragments enhance proliferation indicates that **CTLA4**/B7 interactions inhibit proliferative response of T cells to SEB. Further, anti-**B7-1**/2 **antibodies** augment proliferation in the presence of optimal stimulation with CD28 **antibodies**, providing additional support for the notion that the inhibitory signals are mediated through **CTLA**-4-B7 interactions.

CD28 and **CTLA**-4 Have Opposing Effects on the SEB Induced Expansion of Tcells In vivo. Manipulation of...

3/K/26 (Item 26 from file: 654)

... comparison of wild type (w.t.) and mutant binding ability using

different concentrations of these **CTLA4Ig** fusion proteins. As disclosed in FIG. 7, the mutants are indicated by their respective motif sequences.

FIG. 9 is an **antibody** competition study with the LCL 816 cell line. This figure compares **CTLA4Ig** wild type and mutant protein binding to **CD80** or CD86 in the presence of different concentrations of anti-**CD80** or anti-CD86 **antibody** . As disclosed in FIG. 7, the specific proteins are indicated by their respective motif sequences. ...reagents.

In an additional embodiment of the invention, other reagents, including derivatives reactive with the **CTLA4** mutant molecule are used to regulate T cell interactions. For example, **antibodies**, and/or **antibody** fragments reactive with the **CTLA4** receptor may be screened to identify those capable of inhibiting the binding of the **CTLA4** mutant molecule to the **B7-1** antigen. The **antibodies** or **antibody** fragments such as Fab or F(ab') sub 2 fragments, may then be used to...
...with the T cells, for example, to inhibit T cell proliferation.

In another embodiment, the **CTLA4** mutant molecule may be used to identify additional compounds capable of regulating the interaction between ...the invention.

EXAMPLE 1

By site-specific and homolog mutagenesis, we have identified regions in **CTLA4Ig** which are required for its high avidity binding to **B7-1**. The following is a description of how to make soluble **CTLA4** /CD28 hybrid fusion proteins which bind B7.

Materials and Methods

Monoclonal **antibodies** (mAbs). Murine Mab's specific for **CTLA4** were prepared and characterized as previously described (Linsley et al. J. Ex. Med., (1992) 176:1595-1604). **Antibody** 9.3 (anti-CD28) has been described previously ((Hansen et al., Immunogenetics 10:247-260 (1980)).

Cell Culture. The preparation of stably transfected **B7-1** positive CHO cells has been previously described (Linsley et al., in J. Exp. Med. 173...CD86. In addition we identify 2 amino acid substitutions at this position which generate mutant **CTLA4Ig** molecules that have the ability to bind CD80 in a manner similar to the wild...

... the ability to bind CD86. The following is a description of how to make soluble **CTLA4** fusion proteins which bind **CD80** but not CD86.

Materials and Methods

Monoclonal **antibodies** (mAbs). Murine monoclonal **antibodies** specific for **CD80** and CD86 have been described previously (Kuchroo et al., Cell, Vol. 80, 707-718, (1995).

Cell Culture. The preparation of stably transfected **B7-1** (**CD80**) positive CHO cells has been previously described (Linsley et al., in J. Exp. Med. 173...on the surface of the cell line LCL 816. This mutant's specificity for the **CD80** molecule is demonstrated in competition studies where its binding is inhibited by monoclonal **antibodies** which are specific for **CD80**. Further, **antibodies** specific for CD86 have no effect on this molecule's ability to bind to this cell line.

This data clearly demonstrates that the first tyrosine in the MYPPPY motif in **CTLA4Ig** plays a critical role in this molecule's ability to bind both CD80 and CD86...

3/K/27 (Item 27 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... that there are at least 2 ligands for the CD28 molecule on professional APC, named **B7-1** and B7-2 (Freeman et al., Science, 262, 909 (1993)). It is known that both these molecules can provide a co-stimulatory signal for the activation of T cells.

Monoclonal **antibody** B7-24 is an unique monoclonal **antibody** that binds specifically to the **B7-1** molecule, but not to B7-2. This is in contrast with a recombinant fusion protein of the **CTLA**-4 molecule (Linsley, J. Exp. Med., 174, 561 (1991), which binds to both **B7-1** and B7-2. Monoclonal **antibody** B7-24 is also different from the anti-B7 monoclonal **antibody** BB-1, which binds to **B7-1** and in addition to a third form of the B7 molecule, B7-3 (Boussiotis et... The complex is formed in a manner that blocks the normal signal transduction pathway of **B7-1** through the CD28 or **CTLA4** antigen. Molecules which bind to the B7 antigen include CD28, **CTLA4**, **CTLA4Ig** and anti-B7 **antibodies**.

II. Generating **Antibodies** to Membrane-Associated Antigen Molecules

This section describes a method for generating and selecting antibodies ... GVHD, or rheumatoid arthritis. The two components are: (1) a molecule that binds to the **B7-1** antigen such as MAb B7-24; and (2) an immunosuppressive agent. Molecules that bind to the **B7-1** antigen include CD28, **CTLA4**, **CTLA4Ig** and anti-B7 **antibodies** as described in Section III above.

The anti **B7-1 antibodies** of the invention (or other molecules that bind to the B7-1 antigen) are givenMonoclonal **antibody** B7-24 binds to a different antigenic epitope on the **B7-1** molecule than the BB-1 monoclonal **antibody** and the **CTLA**-4 Ig fusion protein: B7-24 does not bind to B7-2, whereas **CTLA**-4 Ig does; B7-24 and **CTLA**-4 Ig do not bind to **B7-1** negative cells, which are positive for staining with BB-1 monoclonal **antibody**. [Boussiotis et al., Proc. Nat'l. Acad. Sci. (USA), 90, 11059 (1993); and Freeman et...needed for tolerance induction and the blocking effect at day 2 is due to blocking **B7-1**. With the B7-24 **antibody**, this is not a problem because in contrast to **CTLA**-4 Ig, it does not block B7-2. With respect to tolerance induction versus suppression combination of anti-**B7-1** with CsA is

3/K/28 (Item 28 from file: 654)
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... immunosuppression can be used. Such agents may include inhibitors of costimulatory molecules (e.g., a **CTLA4Ig** fusion protein, soluble CD4, anti-CD4 **antibodies**, anti-**B7-1** and/or anti-B7-2 **antibodies** or anti-gp39 **antibodies**).

Finally, in certain situations, a delivery vehicle for cells expressing a therapeutic gene can be...

```
 s (B7 or b7(w)1) and antibod? and (ctla(w)4)

Processing
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            8677  B7
         9423137  1
            2267  B7(W)1
         1052581  ANTIBOD?
            1718  CTLA
         5440798  4
            1540  CTLA(W)4
      S7     342  (B7 OR B7(W)1) AND ANTIBOD? AND (CTLA(W)4)
? s s7 and cd28

             342  S7
            6473  CD28
      S8     301  S7 AND CD28
? s s8 and (inhibit? or block? or suppress?)

Processing
             301  S8
         2240818  INHIBIT?
          958482  BLOCK?
          463481  SUPPRESS?
      S9     232  S8 AND (INHIBIT? OR BLOCK? OR SUPPRESS?)
? s s9 and epitope?

             232  S9
          112881  EPITOPE?
     S10       8  S9 AND EPITOPE?
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>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
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 11/7/1     (Item 1 from file: 55)
DIALOG(R)File  55:BIOSIS PREVIEWS(R)
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14257674     BIOSIS Number: 01257674
  Detection of a soluble form of B7-1 (CD80) in synovial fluid
from patients with arthritis using monoclonal antibodies against
distinct epitopes of human B7-1
  McHugh R S; Ratnoff W D; Gilmartin R; Sell K W; Selvaraj P
  Dep. Pathol. and Lab. Med., Emory Univ. Sch. Med., Atlanta, GA 30322, USA
  Clinical Immunology and Immunopathology 87 (1). 1998.  50-59.
  Full Journal Title:  Clinical Immunology and Immunopathology
  ISSN: 0090-1229
  Language: ENGLISH
  Print Number: Biological Abstracts Vol. 105 Iss. 012 Ref. 170022
  The  costimulatory  molecule B7-1 (CD80) has been shown to be
an  important  component  for  T  cell  immune responses. We have generated
several  monoclonal  antibodies  (PSRM-1, -2, -3, -6, and -7) against
B7-1  using  a  human  glycosylphosphatidylinositol-anchored
```

B7-1 (GPI-**B7-1**) as an antigen. These monoclonal **antibodies** are able to detect **B7-1** by flow cytometry, ELISA, and Western blotting. One **antibody** in particular, PSRM-3, **blocks** the **CD28/CTLA-4** interaction with **B7-1** and consequently **blocks** costimulation of T cells. The other PSRM monoclonal **antibodies** did not compete with PSRM-3 for recognition of **B7-1** and also failed to **block B7-1** interaction with **CTLA-4** and **CD28**, indicating that these **antibodies** bind to different **epitopes**. PSRM-3 and -7 detect phosphatidylinositol-specific phospholipase C-released soluble GPI-**B7-1** in a sandwich ELISA. We used this sandwich ELISA to assay for the presence of a soluble form of **B7-1** in synovial fluids of arthritis patients. By sandwich ELISA, **B7-1** was detected in the synovial fluid of 5/11 patients with rheumatoid arthritis, 5/5 patients with osteoarthritis, and 2/6 patients with other forms, including crystalline-induced arthritis. The presence of soluble **B7-1** was confirmed by immunoprecipitation using PSRM-3-coupled Sepharose beads. The source and function of soluble **B7-1** are unknown at present; it is possible, however, that the soluble form of **B7-1** molecule may play a local immunoregulatory role which may **suppress** or induce inflammation depending upon whether it interacts with the T cell costimulatory **CD28** molecule or the negative signaling **CTLA-4** molecule.

11/7/2 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09207121 95378786
Identification of residues in the V domain of CD80 (**B7-1**) implicated in functional interactions with **CD28** and CTLA4.
Fargeas CA; Truneh A; Reddy M; Hurle M; Sweet R; Sekaly RP
Laboratoire d'Immunologie, Institut de Recherches Cliniques de Montreal, Quebec, Canada.
J Exp Med (UNITED STATES) Sep 1 1995, 182 (3) p667-75, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The CD80 (**B7-1**) molecule is a 45-60-kD member of the immunoglobulin superfamily that is expressed on a variety of cell types of haematopoietic origin. CD80 can provide a critical costimulatory signal to T cells by interacting with the T cell surface molecule **CD28**. CD80 also binds to the **CD28**-related molecule CTLA4, which is expressed on activated T cells, Recently, additional ligands of **CD28** and CTLA4 have been described in mice and humans. One of them, CD86 (B-70 or **B7-2**) was characterized at the molecular level. Although similar in predicted structure to CD80, it is distantly related in amino acid sequence. In this study, human CD80 mutants were generated and tested for their ability to maintain the interaction with **CD28** leading to adhesion and enhanced IL-2 production. Two hydrophobic residues in the V-like domain of CD80 were identified as critical for binding to **CD28** and are also important for the interaction with CTLA4. These residues are adjacent to the **epitope** of the BB1 **antibody**, which **inhibits CD28**-CD80 interactions. One of these residues, Y87, is conserved in all CD80 and CD86 cloned from various species. These results being to unravel the structural requirements for binding to **CD28** and CTLA4.

11/7/3 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09000402 97278843
Induction of peripheral T cell tolerance in vivo requires **CTLA-**

4 engagement.
Perez VL; Van Parijs L; Biuckians A; Zheng XX; Strom TB; Abbas AK
Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA.
Immunity (UNITED STATES) Apr 1997, 6 (4) p411-7, ISSN 1074-7613 Journal Code: CCF
Contract/Grant No.: AI35297, AI, NIAID; AI25022, AI, NIAID; AI37798, AI, NIAID; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Studies of T cell anergy in vitro have led to the widely accepted view that anergy is induced by T cell antigen recognition without costimulation. We show that the induction of T cell anergy in vivo is due to an abortive T cell response that requires recognition of **B7** molecules, since **blocking B7** maintains T cells in an unactivated but functionally competent state. Furthermore, the induction of anergy is prevented by **blocking CTLA-4**, the **inhibitory** T cell receptor for **B7** molecules. Thus, in vivo T cell anergy may be induced not because of a lack of costimulation, but as a result of specific recognition of **B7** molecules by **CTLA-4**. In contrast, **blocking CD28** on T cells prevents priming but not the induction of tolerance. Therefore, the outcome of antigen recognition by T cells is determined by the interaction of **CD28** or **CTLA-4** on the T cells with **B7** molecules.

11/7/4 (Item 3 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08806566 97032622
Blockade of multiple costimulatory receptors induces hyporesponsiveness: **inhibition** of CD2 plus **CD28** pathways.
Woodward JE; Qin L; Chavin KD; Lin J; Tono T; Ding Y; Linsley PS; Bromberg JS; Baliga P
Department of Microbiology and Immunology, Medical University of South Carolina, Charleston 29425, USA.
Transplantation (UNITED STATES) Oct 15 1996, 62 (7) p1011-8, ISSN 0041-1337 Journal Code: WEJ
Contract/Grant No.: AI 32655, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
T-lymphocyte activation requires engagement of the T cell receptor with antigen-major histocompatibility complex, and simultaneous ligation of costimulatory pathways via the lymphocyte receptors CD2 and **CD28**/CTLA4. Anti-CD2 monoclonal **antibody** (mAb) **blocks** the interaction of the antigen-presenting cell receptor CD48 with its ligand CD2, whereas CTLA4Ig binds with high affinity to the antigen-presenting cell ligands **B7-1** and **B7**-2, **blocking** their interaction with **CD28**/CTLA4. We tested the immunosuppressive effects of simultaneously **blocking** both costimulatory pathways. Using donor C57BL/6J (H2b) hearts transplanted to CBA/J (H2k) recipients, anti-CD2 mAb plus CTLA4Ig administered at the time of transplantation prolonged cardiac allograft mean survival time to >120 days compared with untreated controls (12.2+/-0.5 days, P<0.01), anti-CD2 mAb alone (24.8+/-1.0 days, P<0.01), or CTLA4Ig alone (55.0+/-2.0 days, P<0.01). Retransplantation of these recipients with donor-specific and third-party grafts demonstrated that hyporesponsiveness and tolerance were achieved. In vitro stimulation of lymphocytes from tolerant recipients with donor-specific alloantigen resulted in normal cytotoxic T lymphocyte and mixed lymphocyte reaction responses, showing that clonal deletion or anergy did not occur, but that graft adaptation or **suppression** likely helped to maintain long-term graft survival. In vitro combinations of anti-CD2 mAb and CTLA4Ig **suppressed** the generation of allogeneic cytotoxic T lymphocytes (58%) and the mixed lymphocyte reaction (36%); CTLA4Ig was more effective in this

regard and the two agents were not synergistic. Anti-CD2 mAb and CTLA4Ig **suppressed** mitogen-driven proliferation in differential fashions, suggesting that they affected independent signaling pathways. Anti-CD2 mAb and CTLA4Ig also **inhibited** interleukin (IL)-2, IL-4, and IL-2 receptor (CD25). These data indicate that anti-CD2 mAb plus CTLA4Ig induces hyporesponsiveness and tolerance. The mechanism is likely related to the initial disruption of independent pathways of T-lymphocyte activation leading to antigen-specific long-term graft survival.

11/7/5 (Item 4 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08538935 96162441
A T cell lymphoma can provide potent co-stimulatory effects to T cells that are not mediated by **B7-1**, **B7**-2, CD40, HSA or CD70.
Nieland JD; Kruisbeek AM
Division of Immunology, The Netherlands Cancer Institute, Amsterdam.
Int Immunol (ENGLAND) Nov 1995, 7 (11) p1827-38, ISSN 0953-8178
Journal Code: AY5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Dominant second signals for T cell activation can be generated through interactions between **CD28** and **CTLA-4** on T cells with their co-stimulatory ligands **B7-1** and **B7** -2 on APC. Nevertheless, some **B7**-negative cell lines appear capable of providing second signals to T cells, illustrating that **B7** -independent co-stimulatory pathways may exist. One such cell line, the peptide-transporter defective T lymphoma RMA-S, was investigated in the present study, to determine the origin of the co-stimulatory effects it provides. RMA-S can support clonal expansion of purified CD4 or CD8 T cells from unprimed mice activated with concanavalin A (ConA) or immobilized anti-CD3. Nevertheless, RMA-S does not express **B7-1** or **B7** -2, nor does it express other known co-stimulatory molecules, i.e. CD40, gp39, CD70 and HSA. Also, co-stimulation provided by RMA-S could not be **blocked** by **antibodies** or fusion proteins specific for these co-stimulatory molecules, excluding their participation. However, RMA-S' co-stimulatory activity is dependent on adhesive interactions. RMA-S is incapable of IL-2 production in the presence of ConA or anti-CD3, but T cells co-stimulated by RMA-S produce IL-2 and IFN-gamma upon anti-CD3- or ConA-induced activation. Furthermore, co-stimulation of antigen-specific T cell proliferation of both class I- and class II-restricted T cell clones can be provided by RMA-S, and RMA-S can preclude induction of anergy by 1-ethyl-3-(3-dimethyl amino propyl)carboiimide-fixed APC in a class II-restricted T cell clone. The results suggest that potent co-stimulatory pathways can be induced by cellular interactions between a T lymphoma, RMA-S and T cells, not involving gp39, CD40, CD70, HSA, **B7-1** (CD80) or **B7**-2 (CD86). Characterization of the molecules involved is in progress.

11/7/6 (Item 5 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08417908 95378791
CD2 regulates responsiveness of activated T cells to interleukin 12 [published erratum appears in J Exp Med 1995 Oct 1;182(4):1175]
Gollob JA; Li J; Reinherz EL; Ritz J
Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, Massachusetts 02115, USA.
J Exp Med (UNITED STATES) Sep 1 1995, 182 (3) p721-31, ISSN 0022-1007
Journal Code: I2V
Contract/Grant No.: AI21226, AI, NIAID; CA41619, CA, NCI

Languages: ENGLISH
Document type: JOURNAL ARTICLE

Interleukin (IL) 12 is a 70-kD heterodimeric cytokine produced by antigen-presenting cells (APCs) such as macrophages in response to infectious pathogens and interferon (IFN) gamma. The varied immunomodulatory effects of IL-12 include the stimulation of proliferation and IFN-gamma production by T cells, and it also has a central role in the development of the T helper cell type 1 immune phenotype. We undertook the production of **antibodies** capable of modulating the response of T cells to IL-12, and in the process we discovered two **antibodies** that **inhibited** the ability of IL-12 to stimulate T cell proliferation. In this report, we demonstrate that these anti-bodies recognize CD2, and we show how **antibodies** directed toward either the adhesion domain of CD2 or its ligand, CD58, specifically **inhibit** IL-12 induced proliferation and IFN-gamma production by phytohemagglutinin-activated T cells, leaving the response to IL-12 unaffected. A three-to fourfold reduction in proliferation and IFN-gamma production was observed at IL-12 concentrations as high as 1 nM, with complete **inhibition** occurring at < or = 1 pM. This novel effect is not directly mediated at the level of the IL-12 receptor, as shown by the inability of these **antibodies** to **block** IL-12 binding to activated T cells. Furthermore, by using activating pairs of CD2 **antibodies** , we show that CD2 stimulation strongly synergizes with IL-12, even at 0.1 pM, in inducing both T cell proliferation and IFN-gamma production. Cytolytic T lymphocyte-associated antigen 4-immunoglobulin-mediated **inhibition** of the **B7/ CD28** interaction did not affect the T cell response to either IL-12 or IL-2, but the removal of APCs selectively diminished the proliferative response to IL-12. Based on this data, we hypothesize that CD2 has a central role in an IL-12/IFN-gamma positive feedback loop between T cell and APC, providing the key functional link via a CD2/CD58 interaction that controls T cell responsiveness to IL-12. This model provides a basis for future investigations aimed at defining the signaling mechanisms that mediate this cytokine-specific regulatory effect of CD2, and it offers insight into how a cytokine receptor and distinct adhesion molecule can interact to modulate responsiveness to that cytokine. In addition, it underscores the possibility that the clinical potential of an immunomodulatory drug like IL-12 may be governed by the presence or absence of specific costimulation.

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S4          3   RD S3 (unique items)
S5          6   (B7 OR B7(W)1) AND 133 AND ANTIBOD?
S6          3   RD S5 (unique items)
S7        342   (B7 OR B7(W)1) AND ANTIBOD? AND (CTLA(W)4)
S8        301   S7 AND CD28
S9        232   S8 AND (INHIBIT? OR BLOCK? OR SUPPRESS?)
S10         8   S9 AND EPITOPE?
S11         6   RD S10 (unique items)
? s s9 and differential

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        493901  DIFFERENTIAL
     S12    11  S9 AND DIFFERENTIAL
? rd s12

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>>>Records from unsupported files will be retained in the RD set.
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13/7/1 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

12008182 BIOSIS Number: 98608182
Preferential dependence of autoantibody production in murine lupus on CD86 co-stimulatory molecule
Nakajima A; Azuma M; Kodera S; Nuriya S; Terashi A; Abe M; Hirose S; Shirai T; Yagita H; Okumura K
Dep. Immunol., Juntendo Univ. Sch. Med., 2-1-1 Hongo, Bunkyo-ku, Tokyo 113, Japan
European Journal of Immunology 25 (11). 1995. 3060-3069.
Full Journal Title: European Journal of Immunology
ISSN: 0014-2980
Language: ENGLISH
Print Number: Biological Abstracts Vol. 101 Iss. 003 Ref. 035887
Blockade of the interactions between **CD28/CTLA-4** and their ligands, CD80 (**B7**, **B7.1**)/CD86 (B70, **B7**.2), seems an attractive means of induce antigen-specific peripheral tolerance in organ transplantation and autoimmune disease. Recently, diversities between CD80 and CD86 in expression, regulation, and function have been reported in certain cell populations and murine experimental disease models. To investigate the possible **differential** role of CD80 and CD86 in the development of lupus, we treated lupus-prone NZB/W F1 mice with specific monoclonal **antibodies** (mAb) against CD80, CD86, or both. The treatment with a combination of anti-CD80 and CD86 mAb before the onset of lupus completely prevented autoantibody production and nephritis, and prolonged survival. Interestingly, we found that anti-CD86 mAb alone, but not anti-CD80 mAb, efficiently **inhibited** autoantibody production. Subclass study on IgG anti-double-stranded (ds) DNA **antibody** revealed that the treatment with anti-CD86 mAb almost completely **inhibited** both IgG1 and IgG2b, but not IgG2a production. The incomplete reduction of IgG2a anti-dsDNA **antibody** by anti-CD86 mAb was compensated by the addition of anti-CD80 mAb. A significant reduction of mRNA for interleukin (IL)-2, interferon-gamma, IL-4 and IL-6 was observed in mice treated with a combination of anti-CD80 and CD86 mAb or anti-CD86 mAb alone. Treatment with both mAb after the onset of lupus resulted in a significantly prolonged survival with reduction of autoantibody production. These results suggest that CD86 plays a more critical role in autoantibody production, and CD86, but not CD80, contributes to Th2-mediated Ig production. However, the **blockade** of both CD80 and CD86 are required for preventing the development and progression of lupus.

13/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

11039351 BIOSIS Number: 97239351
Expression and function of the costimulatory molecule **B7** on murine Langerhans cells: Evidence for an alternative **CTLA-4** ligand
Razi-Wolf Z; Falo L D Jr; Reiser H
Div. Lymphocyte Biol., Dana-Farber Cancer Inst., 44 Binney St., Boston, MA 02115, USA
European Journal of Immunology 24 (4). 1994. 805-811.
Full Journal Title: European Journal of Immunology
ISSN: 0014-2980
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 011 Ref. 156460
We have previously shown, through transfection experiments, that the murine **B7** (mB7) molecule, a ligand for the **CD28** and **CTLA-4** receptors, is a sufficient costimulatory signal for the

antigen-specific and major histocompatibility complex (MHC)-restricted activation of murine CD4+ T lymphocytes. In addition to mB7, another ligand with affinity for **CTLA-4** has been described on spleen cells. Here we report our studies on the expression and function of these molecules on murine Langerhans cells (LC). Both anti-mB7 monoclonal **antibody** (mAb) 16-10A1 and human CTLA4Ig (hCTLA4Ig), a chimeric fusion protein consisting of the extracellular domain of human CLTA-4 and the constant domain of human IgG1, detected antigens(s) on cultured but not freshly isolated LC. Preincubation of cultured LC with anti-mB7 mAb did not significantly affect binding of hCTLA4Ig to these cells. This result demonstrate the existence of at least one other ligand for the CLTA-4 receptor on cultured LC. Functional studies revealed that the costimulatory activity of LC was **inhibited** better by hCTLA4Ig than by the anti-mB7 mAb. This **differential** effect was seen in the case of both alloreactive and antigen-specific, syngeneic T cell responses. These findings suggest that the non-mB7-ligand for **CTLA-4** is functional and participates in the induction of immune responses by LC. Importantly, even synergistic combinations of anti-mB7 mAb and hCTLA4Ig did not **inhibit** completely the activity of LC. These findings therefore raise the possibility that LC express other costimulatory ligands besides mB7 and related family members.

13/7/3 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10173399 EMBASE No: 96361667
The role of CD 80 and CD 86 costimulatory molecules in autoimmunity and tumor immunity
Azuma M.; Nakajima A.
Department of Immunology, Natl. Children's Med. Res. Center, 3-35-31 Taishido, Setagaya-ku, Tokyo 154 Japan
Biotherapy (Japan) , 1996, 10/10 (1261-1266)
CODEN: BITPE ISSN: 0914-2223
LANGUAGES: Japanese SUMMARY LANGUAGES: English; Japanese
Immune responses in tumor bearing host and patients with autoimmune disease are triggered by antigen-specific T cell responses and modified by subsequent cellular and humoral immune responses. It is increasingly clear that antigen-specific T-cell activation requires the engagement of the T-cell receptor with antigen/MHC as well as engagement of appropriate costimulatory molecules. The most characterized costimulatory molecules are CD 28/**CTLA-4** on T cells and their ligands, CD 80/CD 86 on antigen-presenting cells. Recent reports suggested the possibilities that inappropriate expression of **CTLA-4** ligands induces autoimmunity and **blockade** of CD 28 pathway prevents development of autoimmune diseases, based on studies using CD 80 transgenic mice and murine models treated with CTLA4Ig fusion protein or monoclonal **antibodies** against CD 80 and CD 86. We here report the **differential** role of CD 80 and CD 86 costimulatory molecules in the development of autoimmunity and discuss the possible implications for autoimmune therapy as well as tumor immunity by manipulating costimulatory molecules.

13/7/4 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

9440162 EMBASE No: 95006493
CD80 (**B7**) and CD86 (B70) provide similar costimulatory signals for T cell proliferation, cytokine production, and generation of CTL
Lanier L.L.; O'Fallon S.; Somoza C.; Phillips J.H.; Linsley P.S.; Okumura K.; Ito D.; Azuma M.
Department of Human Immunology, DNAX RIMCB, Inc., 901 California Avenue, Palo Alto, CA 94304 USA

J. IMMUNOL. (USA) , 1995, 154/1 (97-105)
CODEN: JOIMA ISSN: 0022-1767
LANGUAGES: English SUMMARY LANGUAGES: English

Signals initiated through both the TCR complex and **CD28** are required for optimal activation of T lymphocytes. Recently, it has been demonstrated that **CD28** interacts with two different ligands, designated CD80 (**B7**/**B7-1**) and CD86 (B70/**B7**-2). We have produced stable transfectants that express CD80, CD86, or both ligands and have examined their ability to costimulate T cell proliferation, cytokine production, and the generation of CTL. When we used small, resting human peripheral blood T cells as responders, both CD80 and CD86 transfectants efficiently costimulated anti-CD3 mAb-induced proliferation and the secretion of IL-2 and IFN-gamma. Additionally, both CD80 and CD86 transfectants were able to generate functional CTL. The magnitude and kinetics of these responses were similar, which indicates that both ligands provide efficient costimulatory signals. Because many APCs coexpress both CD80 and CD86, we compared the ability of anti-CD80 and anti-CD86 mAbs to **inhibit** allogeneic MLR stimulated with B lymphoblastoid cell lines and showed that it is necessary to **inhibit** interactions with both ligands to optimally **block** **CD28**-dependent proliferation. Given the limited homology of CD80 and CD86, it was surprising that the binding of **CD28**-Ig fusion protein to CD80 and that to CD86 transfectants were essentially indistinguishable. Binding of **CTLA-4** -Ig fusion protein to both transfectants also was quite similar, but was of higher affinity than **CD28** -Ig binding. Results from these studies indicate that both CD80 and CD86 are potent and similar costimulators of T lymphocytes. Therefore, the role of CD80 and CD86 in an immune response may be determined primarily by their **differential** expression on APC.

13/7/5 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08806566 97032622

Blockade of multiple costimulatory receptors induces hyporesponsiveness: **inhibition** of CD2 plus **CD28** pathways.

Woodward JE; Qin L; Chavin KD; Lin J; Tono T; Ding Y; Linsley PS; Bromberg JS; Baliga P

Department of Microbiology and Immunology, Medical University of South Carolina, Charleston 29425, USA.

Transplantation (UNITED STATES) Oct 15 1996, 62 (7) p1011-8, ISSN 0041-1337 Journal Code: WEJ

Contract/Grant No.: AI 32655, AI, NIAID

Languages: ENGLISH

Document type: JOURNAL ARTICLE

T-lymphocyte activation requires engagement of the T cell receptor with antigen-major histocompatibility complex, and simultaneous ligation of costimulatory pathways via the lymphocyte receptors CD2 and **CD28**/CTLA4. Anti-CD2 monoclonal **antibody** (mAb) **blocks** the interaction of the antigen-presenting cell receptor CD48 with its ligand CD2, whereas CTLA4Ig binds with high affinity to the antigen-presenting cell ligands **B7-1** and **B7**-2, **blocking** their interaction with **CD28**/CTLA4. We tested the immunosuppressive effects of simultaneously **blocking** both costimulatory pathways. Using donor C57BL/6J (H2b) hearts transplanted to CBA/J (H2k) recipients, anti-CD2 mAb plus CTLA4Ig administered at the time of transplantation prolonged cardiac allograft mean survival time to >120 days compared with untreated controls (12.2+/-0.5 days, P<0.01), anti-CD2 mAb alone (24.8+/-1.0 days, P<0.01), or CTLA4Ig alone (55.0+/-2.0 days, P<0.01). Retransplantation of these recipients with donor-specific and third-party grafts demonstrated that hyporesponsiveness and tolerance were achieved. In vitro stimulation of lymphocytes from tolerant recipients with donor-specific alloantigen resulted in normal cytotoxic T lymphocyte and mixed lymphocyte reaction responses, showing that clonal deletion or anergy did not occur, but that

graft adaptation or **suppression** likely helped to maintain long-term graft survival. In vitro combinations of anti-CD2 mAb and CTLA4Ig **suppressed** the generation of allogeneic cytotoxic T lymphocytes (58%) and the mixed lymphocyte reaction (36%); CTLA4Ig was more effective in this regard and the two agents were not synergistic. Anti-CD2 mAb and CTLA4Ig **suppressed** mitogen-driven proliferation in **differential** fashions, suggesting that they affected independent signaling pathways. Anti-CD2 mAb and CTLA4Ig also **inhibited** interleukin (IL)-2, IL-4, and IL-2 receptor (CD25). These data indicate that anti-CD2 mAb plus CTLA4Ig induces hyporesponsiveness and tolerance. The mechanism is likely related to the initial disruption of independent pathways of T-lymphocyte activation leading to antigen-specific long-term graft survival.

13/7/6 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08767321 96324743
Differential requirements for co-stimulatory signals from **B7** family members by resting versus recently activated memory T cells towards soluble recall antigens.
Yi-qun Z; Joost van Neerven RJ; Kasran A; de Boer M; Ceuppens JL
Laboratory of Experimental Immunology, Department of Pathophysiology, Catholic University of Leuven, Leuven, Belgium.
Int Immunol (ENGLAND) Jan 1996, 8 (1) p37-44, ISSN 0953-8178
Journal Code: AY5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The interaction between **CD28** on T cells with CD80 (**B7-1**) and CD86 (**B7**-2) on APCs is considered to be of critical importance for primary T cell activation both in vivo and in vitro. The relative importance of this co-stimulatory signal in memory T cell activation is, however, less clear, and was therefore studied by in vitro experiments on T cell responses to soluble recall antigens using peripheral blood mononuclear cells or T cell clones. Our data demonstrate that **B7**-2 represents the major co-stimulatory signal for the activation of resting peripheral blood memory T cells with recall antigens, as evidenced by the effects of anti-**B7-1** and anti-**B7** -2 on T cell proliferation as well as on IL-2 and INF-gamma production. Since **CTLA-4**-lg and anti-**CD28** Fab fragments had similar **inhibitory** effects to the combination of anti-**B7-1** plus anti **B7**-2, the involvement of a third co-stimulatory **CD28/CTLA-4** ligand is unlikely. Despite the strong effects of **B7-blocking** agents, a variable fraction of the memory T cells was resistant to **inhibition** . Moreover, T cell clones or in vitro preactivated T cells could efficiently be restimulated by soluble atigens on autologous APCs in the absence of **B7-1** or **B7**-2 co-stimulation. These data show that most memory T cells that are freshly isolated from the blood are still dependent on **CD28** triggering for their activation. However, recently activated T cells can apparently bypass the requirement for **B7** and use other co-stimulatory signals for reactivation, a finding with important implications for the development of immunosuppressive strategies.

13/7/7 (Item 3 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08410399 95173582
Differential effects of anti-**B7-1** and anti-**B7**-2 monoclonal **antibody** treatment on the development of diabetes in the nonobese diabetic mouse.
Lenschow DJ; Ho SC; Sattar H; Rhee L; Gray G; Nabavi N; Herold KC;

Bluestone JA
Ben May Institute, Chicago, Illinois 60637.
J Exp Med (UNITED STATES) Mar 1 1995, 181 (3) p1145-55, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: GM07183-19, GM, NIGMS; P60 DK20595, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Insulin-dependent diabetes mellitus (IDDM) is thought to be an immunologically mediated disease resulting in the complete destruction of the insulin-producing islets of Langerhans. It has become increasingly clear that autoreactive T cells play a major role in the development and progression of this disease. In this study, we examined the role of the **CD28/B7** costimulation pathway in the development and progression of autoimmune diabetes in the nonobese diabetic (NOD) mouse model. Female NOD mice treated at the onset of insulitis (2-4 wk of age) with CTLA4Ig immunoglobulin (Ig) (a soluble **CD28** antagonist) or a monoclonal **antibody** (mAb) specific for **B7**-2 (a **CD28** ligand) did not develop diabetes. However, neither of these treatments altered the disease process when administered late, at > 10 wk of age. Histological examination of islets from the various treatment groups showed that while CTLA4Ig and anti-**B7**-2 mAb treatment **blocked** the development of diabetes, these reagents had little effect on the development or severity of insulitis. Together these results suggest that **blockade** of costimulatory signals by CTLA4Ig or anti-**B7**-2 acts early in disease development, after insulitis but before the onset of frank diabetes. NOD mice were also treated with mAbs to another **CD28** ligand, **B7-1**. In contrast to the previous results, the anti-**B7-1** treatment significantly accelerated the development of disease in female mice and, most interestingly, induced diabetes in normally resistant male mice. A combination of anti-**B7-1** and anti-**B7** -2 mAbs also resulted in an accelerated onset of diabetes, similar to that observed with anti-**B7-1** mAb treatment alone, suggesting that anti-**B7-1** mAb's effect was dominant. Furthermore, treatment with anti-**B7-1** mAbs resulted in a more rapid and severe infiltrate. Finally, T cells isolated from the pancreas of these anti-**B7-1** -treated animals exhibited a more activated phenotype than T cells isolated from any of the other treatment groups. These studies demonstrate that costimulatory signals play an important role in the autoimmune process, and that different members of the **B7** family have distinct regulatory functions during the development of autoimmune diabetes.

? ds

Set	Items	Description
S1	17	E1,E5,E6
S2	17	RD S1 (unique items)
S3	7	(B7 OR B7(W)1) AND (7B6 OR 16C10 OR 7C10 OR 20C9)
S4	3	RD S3 (unique items)
S5	6	(B7 OR B7(W)1) AND 133 AND ANTIBOD?
S6	3	RD S5 (unique items)
S7	342	(B7 OR B7(W)1) AND ANTIBOD? AND (CTLA(W)4)
S8	301	S7 AND CD28
S9	232	S8 AND (INHIBIT? OR BLOCK? OR SUPPRESS?)
S10	8	S9 AND EPITOPE?
S11	6	RD S10 (unique items)
S12	11	S9 AND DIFFERENTIAL
S13	7	RD S12 (unique items)

? s s9 and (different?)(20n)(cd28) and

>>>Possible typing error near end of command
? s s9 and (different?)(20n)(cd28)(20n)(ctla(w)4)

232 S9
2861445 DIFFERENT?

```
             6473  CD28
             1718  CTLA
          5440798  4
              233  DIFFERENT?(20N)CD28(20N)CTLA(W)4
     S14       58  S9 AND (DIFFERENT?)(20N)(CD28)(20N)(CTLA(W)4)
? rd s14

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>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...completed examining records
     S15       53  RD S14 (unique items)
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DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ********
ENTER PASSWORD:
□p58093fe
 ********
Welcome to DIALOG

Dialog level 98.08.06D

Last logoff:  14aug98 16:50:02
Logon file001 15aug98 18:39:46
ANNOUNCEMENT    ****    ANNOUNCEMENT    ****    ANNOUNCEMENT
NEW
***Gannett News Service (File 604)
***UMI Newsstand(TM) (File 781)
***Baton Rouge Advocate (File 382)
***Pharm-line(R) (File 174)
***Federal Register (File 180 - replacing File 669)
                              ***
RELOADED
***SCISEARCH (File 34 accession numbers have changed)
***NTIS (File 6)
***PSYCInfo (File 11)
                              ***
RESTRUCTURED
***SCISEARCH (file 434 is now a backfile)
                              ***
REMOVED
***IAC Industry Express (File 12) - merged into IAC PROMT (file 16)
***UPI News archival (File 260)
***Dialog Quotes and Trading (QUOTES)
***Yellow Books: Corporate & Financial (File 81)
***Yellow Books: Law Firms (File 82)
***Yellow Books: Leadership Index (File 235)
***OAG Electronic Edition(R) Travel Service (File OAG)
***Federal Register (File 669 - replaced by File 180)
                              ***
NEW UK HELP DESK PHONE NUMBER
***Please note that the UK Help Desk telephone number has
   been changed to (0800) 69 00 00.

PRICING CHANGE
The Dialog Corporation Announces Major Price Reductions,
Eliminates DialUnits Rounding Effective September 1, 1998.
See Homebase for complete announcement.

     >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
     >>>    of new databases, price changes, etc.      <<<
     >>>    Announcements last updated 11 August 98    <<<
* * * The ERIC Dialorder supplier now requires prepayment with
* * * all orders. For information contact ERIC document supply
* * * at 800-443-3742 or service@edrs.com.
* * * File 196 is currently unavailable. * * *

File   1:ERIC  1966-1998/May
       (c) format only 1998 The Dialog Corporation
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      Set  Items  Description
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? b 410

       15aug98 18:39:52 User208760 Session D1096.1
            $0.18    0.055 DialUnits File1
     $0.18  Estimated cost File1
            FTSNET   0.001 Hrs.
     $0.18  Estimated cost this search
     $0.18  Estimated total session cost   0.055 DialUnits

File 410:Chronolog(R)  1981-1998/Jul/Aug
       (c) 1998 The Dialog Corporation plc

      Set  Items  Description
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? set hi ;set hi

HILIGHT set on as ''
HILIGHT set on as ''
? begin 55,72,154,399,351

       15aug98 18:40:08 User208760 Session D1096.2
            $0.00    0.107 DialUnits File410
     $0.00  Estimated cost File410
            FTSNET   0.004 Hrs.
     $0.00  Estimated cost this search
     $0.18  Estimated total session cost   0.163 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File  55:BIOSIS PREVIEWS(R)  1985-1998/Aug W2
        (c) 1998 BIOSIS
  File  72:EMBASE  1985-1998/Aug W2
        (c) 1998 Elsevier Science B.V.
  File 154:MEDLINE(R)  1985-1998/Oct W2
        (c) format only 1998 Dialog Corporation
  File 399:CA SEARCH(R)  1967-1998/UD=12907
        (c) 1998 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
RANK charge added; see HELP RATES 399.
  File 351:DERWENT WPI  1963-1998/UD=9832;UP=9829;UM=9827
        (c)1998 Derwent Info Ltd
*File 351: All images are now present.  The display formats have
changed for 1998. See HELP FORM 351 for more information.

      Set  Items  Description
      ---  -----  -----------
? s b7(w)24 and antibod?

          8713  B7
        998619  24
            18  B7(W)24
       1054817  ANTIBOD?
      S1    16  B7(W)24 AND ANTIBOD?
? rd s1

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S2     7  RD S1 (unique items)
? t s2/7/all
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2/7/1 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

13816815 BIOSIS Number: 99816815
B7-1 (CD80) as target for immunotoxin therapy for Hodgkin's disease
Vooijs W C; Otten H G; Van Vliet M; Van Dijk A J G; De Weger R A; De Boer M; Bohlen H; Bolognesi A; Polito L; De Gast G C
Dep. Haematol., HP F03.722, University Hosp. Utrecht, PO Box 85500, 3508 GA Utrecht, Netherlands
British Journal of Cancer 76 (9). 1997. 1163-1169.
Full Journal Title: British Journal of Cancer
ISSN: 0007-0920
Language: ENGLISH
Print Number: Biological Abstracts Vol. 104 Iss. 012 Ref. 174419
In this preclinical study, the potential applicability of an anti-B7-1 immunotoxin (IT) for the treatment of Hodgkin's disease (HD) was investigated. Immunohistochemical analysis demonstrated strong expression of B7-1 on Hodgkin and Reed-Sternberg (R-S) cells and clear expression on dendritic cells, macrophages and some B-cells in tissues, but not on other tissue cells. Flow cytometric analysis demonstrated that B7-1 was expressed on a few monocytes, but not on CD34+ cells from bone marrow, resting T- or B-cells from peripheral blood or epithelial and endothelial cell lines. An anti-B7-1 immunotoxin containing the anti-B7-1 monoclonal **antibody** (MAb) **B7-24** and saporin as toxin moiety was constructed and showed an affinity similar to that shown by the native MAb. It exhibited strong cytotoxicity against the B7-1+ B-cell line Raji (IC-50 10-11 M), R-S cell lines HDLM2, KM/H2 and L428 and also against a B7-1 -transfected epithelial cell line, A431, whose parental line lacks expression of B7-1. In clonogenic assays with Raji cells or KM/H2 cells, a 3- or 4-log kill, respectively, was observed. No cytotoxicity was found against the B7-1- epithelial and endothelial cell lines or against haematopoietic progenitor cells. In conclusion, an anti-B7-1 immunotoxin was developed that had good cytotoxicity against R-S cell lines and that may be used in the elimination of R-S cells in vivo. A concomitant elimination of activated antigen-presenting cells may avoid development of antitoxin and anti-mouse Ig responses and allow repeated administration.

2/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

12116374 BIOSIS Number: 98716374
Generation of humanized Fab fragments of **B7-24** mAb, an **antibody** with potential use in the prevention of graft rejection and development of graft-versus-host disease
Wettendorff M; Blockx H; Dove J; Ring D; Desmet W; De Boer M
Innogenetics, Gent, Belgium
Mededelingen Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen Universiteit Gent 60 (4A-B). 1995. 2057-2063.
Full Journal Title: Ninth Forum for Applied Biotechnology, Gent, Belgium, September 27-29, 1995. Mededelingen Faculteit Landbouwkundige en Toegepaste Biologische Wetenschappen Universiteit Gent
ISSN: *********
Language: ENGLISH
Print Number: Biological Abstracts/RRM Vol. 048 Iss. 004 Ref. 062556

2/7/3 (Item 3 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10928554 BIOSIS Number: 97128554
Synergy between cyclosporin A and a monoclonal **antibody** to B7 in

blocking alloantigen-induced T-cell activation
Van Gool S W; Ceuppens J L; Walter H; De Boer M
Dep. Immunol., Innogenetic NV, Industriepark Zwijnaarde 7, Box 4, B-9052 Ghent, BEL
Blood 83 (1). 1994. 176-183.
Full Journal Title: Blood
ISSN: 0006-4971
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 006 Ref. 078430
Costimulatory signals are absolutely required for T-cell activation after T-cell receptor/major histocompatibility complex-peptide interaction. So far, the best-known candidate essential costimulatory signal is mediated by interaction of CD28 on T cells with B7 on antigen-presenting cells. Using an allogeneic B7+ Epstein-Barr virus-transformed B-cell line as stimulator, we found that addition of a monoclonal **antibody** (MoAb) to B7 that efficiently blocks B7-CD28 interaction only partially inhibited proliferation and interleukin-2 (IL-2) production in primary and secondary mixed lymphocyte reactions (MLR), whereas the generation of cytotoxic T lymphocytes (CTL) was not affected. Inhibition of primary or secondary MLR-induced T-cell activation with cyclosporin A (CsA) at nontoxic concentrations also was never complete. However, the combination of CsA and anti-B7 MoAb **B7-24** synergistically blocked allogeneic B cell-induced T-cell proliferation, IL-2 production, and CTL generation. These data suggest that the mere blockage of B7-CD28 interaction during allotransplantation will be insufficient to prevent rejection or graft-versus-host disease. However, low CsA concentrations, when combined with an agent blocking B7-CD28 interaction, can potentially achieve complete immunosuppression.

2/7/4 (Item 4 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10050740 BIOSIS Number: 95050740
FUNCTIONAL CHARACTERIZATION OF A NOVEL ANTI-B7 MONOCLONAL **ANTIBODY**
DE BOER M; PARREN P; DOVE J; OSSENDORP F; VAN DER HORST G; REEDER J
INNOGENETICS, INDUSTRIEPARK ZWIJNAARDE 7, BOX 4, B-9052 GHENT, BELGIUM.
EUR J IMMUNOL 22 (12). 1992. 3071-3075. CODEN: EJIMA
Full Journal Title: European Journal of Immunology
Language: ENGLISH
For optimal activation of T cells, binding of their T cell receptor to antigenic peptides in the context of major histocompatibility complex molecules on antigen-presenting cells (APC) is not sufficient. Accessory signals, provided by accessory cells, are needed to induce proliferation and clonal expansion of normal T cells. It has been shown previously that the B7 molecule, present on the cell surface of activated APC, can provide the second signal by binding to the CD28 molecule on T cells. Here we describe a novel anti-B7 (mAb), **B7-24**. This mAb binds to a functionally important epitope of the B7 molecule. Fab fragments of **B7-24** can almost completely block anti-CD3-induced, B7-dependent T cell proliferation when tested in a model system where purified T cells are co-cultured with 3T6 cells expressing the human Fc.gamma.RII and human B7, in the presence of anti-CD3 mAb. In contrast, mAb **B7-24** is not able to inhibit T cell proliferation in primary mixed lymphocyte reactions where purified T cells are co-cultured with Epstein-Barr virus-transformed B cells. These findings suggest that other cell surface molecules allow for maximal proliferation of T cells in mixed lymphocyte reactions, even when the interaction between B7 and CD28 is blocked by **B7-24**.

2/7/5 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10797245 EMBASE No: 98225835
Blocking of costimulatory pathways using monoclonal **antibodies** as a new strategy to prevent transplant rejection in a non-human primate model
Ossevoort M.A.; De Boer M.; Lorre K.; Van de Voorde A.; Jonker M.
M.A. Ossevoort, Biomechanical Primate Res. Centre, PO Box 3306, 2280 GH Rijswijk Netherlands
Transplantation Proceedings (United States) , 1998, 30/4 (1061-1062)
CODEN: TRPPA ISSN: 0041-1345
PUBLISHER ITEM IDENTIFIER: S0041134598001511
DOCUMENT TYPE: Journal Conference Paper
LANGUAGES: ENGLISH
NUMBER OF REFERENCES: 6

2/7/6 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

8789065 EMBASE No: 93093170
In situ expression of B7/BB1 on antigen-presenting cells and activated B cells: An immunohistochemical study
Vandenberghe P.; Delabie J.; De Boer M.; De Wolf-Peeters C.; Ceuppens J.L.
Laboratory for Clinical Immunology, University Hospitals St-Raphael, Kapucijnenvoer 33, B-3000 Leuven Belgium
INT. IMMUNOL. (United Kingdom) , 1993, 5/3 (317-321)
CODEN: INIME ISSN: 0953-8178
LANGUAGES: English SUMMARY LANGUAGES: English
B7/BB1 is a physiological ligand for CD28, a receptor expressed on a major subset of T lymphocytes. B7/BB1 has been shown to be expressed on human blood dendritic cells and on in vitro activated (but not resting) B cells and monocytes. Ligation of CD28 with B7/BB1 upregulates cytokine production and prevents the induction of anergy in T cells activated through TCR/CD3. We examined the in situ expression of B7/BB1 by immunohistochemistry with a novel mAb **B7-24**. Dendritic cells in skin (Langerhans cells), lymph node sinuses (veiled cells), and T cell zones of spleen and lymph nodes (interdigitating dendritic cells) were strongly positive for B7/BB1. B7/BB1 was also present on fetal thymus dendritic cells located at the cortico-medullar junction and the medulla, but absent in normal adult thymuses. Resident macrophages and endothelial cells did not stain, but in granulomatous inflammations B7/BB1 was found on macrophages and epitheloid cells. A subset of B immunoblasts and of germinal center B cells in lymph node and spleen was also found to express B7/BB1. Our findings on the distribution of B7/BB1 expression in tissues, in particular its expression on professional antigen-presenting cells, further substantiate the putative co-stimulatory role of B7/BB1 in T cell activation in vivo. The presence of B7/BB1 in fetal but not adult thymic medulla suggests a role for B7/BB1 in thymocyte maturation.

2/7/7 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

010401410
WPI Acc No: 95-302723/199539
T cell anergy induction by coadmin. of anti-B7-**antibody** and immunosuppressive agent - used to prevent transplant rejection, and to treat graft vs host disease and rheumatoid arthritis
Patent Assignee: CETUS ONCOLOGY CORP (CETU); CHIRON CORP (CHIR)
Inventor: CONROY L B; DEBOER M; DE BOER M
Number of Countries: 021 Number of Patents: 005
Patent Family:
Patent No Kind Date Applicat No Kind Date Main IPC Week

WO 9522619	A1	19950824	WO 95US897	A	19950119	C12P-021/08	199539 B
AU 9516877	A	19950904	AU 9516877	A	19950119	C12P-021/08	199549
EP 745136	A1	19961204	EP 95908634	A	19950119	C12P-021/08	199702
			WO 95US897	A	19950119		
JP 9510607	W	19971028	JP 95521804	A	19950119	C12N-015/02	199802
			WO 95US897	A	19950119		
US 5747034	A	19980505	US 92910222	A	19920709	A61K-039/395	199825
			US 9315147	A	19930209		
			US 94200716	A	19940218		

Priority Applications (No Type Date): US 94200716 A 19940218; US 92910222 A 19920709; US 9315147 A 19930209
Cited Patents: 4.Jnl.Ref
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9522619	A1	E	77			
Designated States (National): AU CA JP						
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE						
AU 9516877	A			Based on		WO 9522619
EP 745136	A1	E		Based on		WO 9522619
Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE						
JP 9510607	W		76	Based on		WO 9522619
US 5747034	A			CIP of	US 92910222	
				CIP of	US 9315147	
				CIP of		US 5397703

Abstract (Basic): WO 9522619 A

An Anti-B7-1-specific **antibody** (Ab) which does not bind B7-2 is claimed. Also claimed are: (1) a compsn. comprising a B7-1 ligand and a diluent or carrier; and (2) the monoclonal Ab (MAb) **B7-24**.

USE - The above Ab (which selectively binds the CD28 ligand B7-1) can be used in conjunction with an immunosuppressive agent to prevent transplant rejection, and to treat graft vs host disease and rheumatoid arthritis.

ADVANTAGE - Admin. of the Ab and immunosuppressive agent induces long-lasting T cell anergy against an alloantigen.

Dwg.0/14

Derwent Class: B04; D16
International Patent Class (Main): A61K-039/395; C12N-015/02
International Patent Class (Additional): A61K-031/445; A61K-031/57; A61K-031/71; A61K-038/00; C07H-021/04; C07K-016/18; C07K-016/42; C12N-005/10; C12N-005/12; C12P-021/08; A61K-038-13; A61K-039/395; A61K-031-445; A61K-031-57; C12R-001-91

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? s sl and ctla?

          9434  SL
          2443  CTLA?
     S3      4  SL AND CTLA?
? t s3/3/all


 3/3/1     (Item 1 from file: 72)
DIALOG(R)File  72:EMBASE
(c) 1998 Elsevier Science B.V. All rts. reserv.
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10501527 EMBASE No: 97319344

Protective and therapeutic immunity against leukemia induced by irradiated B7-1 (CD80)-transduced leukemic cells

Hirano N.; Takahashi T.; Takahashi T.; Azuma M.; Okumura K.; Yazaki Y.; Yagita H.; Hirai H.

Dr. H. Hirai, Third Department Internal Medicine, Faculty of Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo Japan

Human Gene Therapy (USA) , 1997, 8/11 (1375-1384)
CODEN: HGTHE ISSN: 1043-0342
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
NUMBER OF REFERENCES: 47

3/3/2 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

10412452 EMBASE No: 97223315
Protective and therapeutic immunity against leukemia induced by irradiated B7-1 (CD80)-transduced leukemic cells
Hirano N.; Takahashi T.; Takahashi T.; Azuma M.; Yazaki Y.; Yagita H.; Hirai H.
N. Hirano, Third Department Internal Medicine, University of Tokyo, Hongo 7-3-1, Bunkyo-ku, Tokyo 113 Japan
Leukemia (United Kingdom) , 1997, 11/SUPPL. 3 (577-581)
CODEN: LEUKE ISSN: 0887-6924
DOCUMENT TYPE: Journal
LANGUAGES: English SUMMARY LANGUAGES: English
NUMBER OF REFERENCES: 30

3/3/3 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09159892 97439576
Protective and therapeutic immunity against leukemia induced by irradiated B7-1 (CD80)-transduced leukemic cells.
Hirano N; Takahashi T; Takahashi T; Azuma M; Okumura K; Yazaki Y; Yagita H; Hirai H
Third Department of Internal Medicine, Faculty of Medicine, University of Tokyo, Japan.
Hum Gene Ther (UNITED STATES) Jul 20 1997, 8 (11) p1375-84, ISSN 1043-0342 Journal Code: A12
Languages: ENGLISH
Document type: JOURNAL ARTICLE

3/3/4 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09101196 97353201
Protective and therapeutic immunity against leukemia induced by irradiated B7-1 (CD80)-transduced leukemic cells.
Hirano N; Takahashi T; Takahashi T; Azuma M; Yazaki Y; Yagita H; Hirai H
Third Department of Internal Medicine, University of Tokyo.
Leukemia (ENGLAND) Apr 1997, 11 Suppl 3 p577-81, ISSN 0887-6924 Journal Code: LEU
Languages: ENGLISH
Document type: JOURNAL ARTICLE

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s

Set     Items   Description
S1         16   B7(W)24 AND ANTIBOD?
S2          7   RD S1 (unique items)
S3          4   SL AND CTLA?
? rd s3

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
      S4       1  RD S3 (unique items)
? s s1 and ctla?

             16  S1
           2443  CTLA?
      S5       1  S1 AND CTLA?
? t s5/7/all


 5/7/1     (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
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08167998   94100531
   Synergy between cyclosporin A and a monoclonal antibody to B7 in
blocking alloantigen-induced T-cell activation.
  Van Gool SW; Ceuppens JL; Walter H; de Boer M
  Department of Pathophysiology, Catholic University of Leuven, Belgium.
  Blood (UNITED STATES)  Jan 1 1994,  83 (1) p176-83,  ISSN 0006-4971
Journal Code: A8G
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE
  Costimulatory signals are absolutely required for T-cell activation after
T-cell receptor/major histocompatibility complex-peptide interaction. So
far, the best-known candidate essential costimulatory signal is mediated by
interaction of CD28 on T cells with B7 on antigen-presenting cells. Using
an allogeneic B7+ Epstein-Barr virus-transformed B-cell line as stimulator,
we found that addition of a monoclonal antibody (MoAb) to B7 that
efficiently blocks B7-CD28 interaction only partially inhibited
proliferation and interleukin-2 (IL-2) production in primary and secondary
mixed lymphocyte reactions (MLR), whereas the generation of cytotoxic T
lymphocytes (CTL) was not affected. Inhibition of primary or secondary
MLR-induced T-cell activation with cyclosporin A (CsA) at nontoxic
concentrations also was never complete. However, the combination of CsA and
anti-B7 MoAb B7-24 synergistically blocked allogeneic B
cell-induced T-cell proliferation, IL-2 production, and CTL generation.
These data suggest that the mere blockage of B7-CD28 interaction during
allotransplantation will be insufficient to prevent rejection or
graft-versus-host disease. However, low CsA concentrations, when combined
with an agent blocking B7-CD28 interaction, can potentially achieve
complete immunosuppression.
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ds

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Set     Items   Description
S1         17   E1,E5,E6
S2         17   RD S1 (unique items)
S3          7   (B7 OR B7(W)1) AND (7B6 OR 16C10 OR 7C10 OR 20C9)
S4          3   RD S3 (unique items)
S5          6   (B7 OR B7(W)1) AND 133 AND ANTIBOD?
S6          3   RD S5 (unique items)
S7        342   (B7 OR B7(W)1) AND ANTIBOD? AND (CTLA(W)4)
S8        301   S7 AND CD28
S9        232   S8 AND (INHIBIT? OR BLOCK? OR SUPPRESS?)
S10         8   S9 AND EPITOPE?
S11         6   RD S10 (unique items)
S12        11   S9 AND DIFFERENTIAL
S13         7   RD S12 (unique items)
? s s9 and (different?)(20n)(cd28) and

>>>Possible typing error near end of command
? s s9 and (different?)(20n)(cd28)(20n)(ctla(w)4)

           232  S9
       2861445  DIFFERENT?
          6473  CD28
          1718  CTLA
       5440798  4
           233  DIFFERENT?(20N)CD28(20N)CTLA(W)4
     S14    58  S9 AND (DIFFERENT?)(20N)(CD28)(20N)(CTLA(W)4)
? rd s14

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...examined 50 records  (50)
...completed examining records
     S15    53  RD S14 (unique items)
? t s15/7/all


 15/7/1     (Item 1 from file: 55)
DIALOG(R)File  55:BIOSIS PREVIEWS(R)
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14315969     BIOSIS Number: 01315969
  Embryonic stem cells and embryoid bodies express lymphocyte costimulatory
molecules
  Ling V; Munroe R C; Murphy E A; Gray G S
  Dep. Immunol. and Hematopoiesis, Genetics Inst., 87 Cambridge Park Drive,
Cambridge, MA 02140, USA
  Experimental Cell Research 241 (1). 1998.  55-65.
  Full Journal Title:  Experimental Cell Research
  ISSN: 0014-4827
  Language: ENGLISH
  Print Number: Biological Abstracts Vol. 105 Iss. 015 Ref. 212246
  Despite  the  importance  of  the costimulatory proteins B7-1
 (CD80),  B7-2  (CD86),  and  their  counterreceptors  CD28 and
CTLA-4 (CD154) in the regulation of T cell proliferation in the
adult immunological system, the initial appearance of these proteins during
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embryonic development has not been investigated. Using in vitro cultures of undifferentiated mouse embryonic stem (ES) cells and **differentiating** embryoid bodies as a model of very early embryonic development, we examined these cells for the presence of mRNA and protein corresponding to the B7 and **CD28** families of costimulatory molecules. By flow cytometry, a stochastically regulated subpopulation of B7-1+ cells comprising 33% of total cells was detected in ES cell cultures, while negligible staining was found for B7-2, **CTLA-4**, and **CD28**. When ES cells were **differentiated** into embryoid bodies for 12 days, a CD45+ subpopulation of embryoid body cells were found to stain positively for B7-1, B7-2, and **CD28** . RT-PCR confirmed cell staining data by revealing amplification products corresponding to B7-1, B7-2, and **CD28** in corresponding samples. Very low levels of **CTLA-4** amplification products were found in all samples; however, surface staining of **CTLA-4** was never detected. The functional capacity of ES cell **B7-1** to bind its ligand was verified by the ability of the soluble fusion protein **CTLA-4** -Ig to bind ES cells and the ability of this reagent to **block** antiB7-1 **antibody** binding in cell based competition assays. These results demonstrate that expression of costimulatory molecules arises very early during in vitro development and suggests that the early embryonic environment may utilize cellular signaling systems analogous to those seen in the immune system.

15/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

14257674 BIOSIS Number: 01257674

Detection of a soluble form of **B7-1** (CD80) in synovial fluid from patients with arthritis using monoclonal **antibodies** against distinct epitopes of human **B7-1**

McHugh R S; Ratnoff W D; Gilmartin R; Sell K W; Selvaraj P
Dep. Pathol. and Lab. Med., Emory Univ. Sch. Med., Atlanta, GA 30322, USA

Clinical Immunology and Immunopathology 87 (1). 1998. 50-59.
Full Journal Title: Clinical Immunology and Immunopathology
ISSN: 0090-1229
Language: ENGLISH
Print Number: Biological Abstracts Vol. 105 Iss. 012 Ref. 170022

The costimulatory molecule **B7-1** (CD80) has been shown to be an important component for T cell immune responses. We have generated several monoclonal **antibodies** (PSRM-1, -2, -3, -6, and -7) against **B7-1** using a human glycosylphosphatidylinositol-anchored **B7-1** (GPI-**B7-1**) as an antigen. These monoclonal **antibodies** are able to detect **B7-1** by flow cytometry, ELISA, and Western blotting. One **antibody** in particular, PSRM-3, **blocks** the **CD28/CTLA-4** interaction with **B7-1** and consequently **blocks** costimulation of T cells. The other PSRM monoclonal **antibodies** did not compete with PSRM-3 for recognition of **B7-1** and also failed to **block B7-1** interaction with **CTLA-4** and **CD28**, indicating that these **antibodies** bind to **different** epitopes. PSRM-3 and -7 detect phosphatidylinositol-specific phospholipase C-released soluble GPI-**B7-1** in a sandwich ELISA. We used this sandwich ELISA to assay for the presence of a soluble form of **B7-1** in synovial fluids of arthritis patients. By sandwich ELISA, **B7-1** was detected in the synovial fluid of 5/11 patients with rheumatoid arthritis, 5/5 patients with osteoarthritis, and 2/6 patients with other forms, including crystalline-induced arthritis. The presence of soluble **B7-1** was confirmed by immunoprecipitation using PSRM-3-coupled Sepharose beads. The source and function of soluble **B7-1** are unknown at present; it is possible, however, that the soluble form of **B7-1** molecule may play a local immunoregulatory role which may **suppress** or induce inflammation depending upon whether it interacts with the T cell costimulatory **CD28** molecule or the negative signaling **CTLA-**

4 molecule.

15/7/3 (Item 3 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10984732 BIOSIS Number: 97184732
Helper effector function of human T cells stimulated by anti-CD3 mAb can be enhanced by co-stimulatory signals and is partially dependent on CD40-CD40 ligand interaction
Kwekkeboom J; De Rijk D; Karsan A; Barcy S; De Groot C; De Boer M
Lab. Cell Biol. Histol., Cellular Immunol. Group, Univ. Amsterdam, Academic Med. Center, Meibergdreef 15, NL-1105 AZ Amsterdam, NET
European Journal of Immunology 24 (3). 1994. 508-517.
Full Journal Title: European Journal of Immunology
ISSN: 0014-2980
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 009 Ref. 118402
In this study we have investigated whether anti-CD3-induced human T cell help for immunoglobulin production could be enhanced by co-stimulation of the T cells via other T cell surface molecules, and the contribution of CD40-CD40 ligand interaction to the execution of T helper effector function induced by these different stimulatory signals. In a system in which irradiated tonsillar T cells were stimulated with immobilized anti-CD3 monoclonal **antibody** (mAb), it was found that ligation of CD2 with a mitogenic pair of mAb considerably enhanced anti-CD3-induced T cell help for immunoglobulin production. Likewise, ligation of **CD28** with mAb enhanced T helper activity, although to a lesser extent. Upon addition of anti-**CD28** and anti-CD2 mAb together, an even higher immunoglobulin production was observed. This combination resulted in a four- to fivefold increase in immunoglobulin production as compared to cultures in which T cells were stimulated with anti-CD3 mAb alone. The effect of ligation with **B7**, the natural ligand of **CD28**, was studied in a system which utilizes the presentation of anti-CD3 mAb on human Fc-gamma-RII-expressing mouse fibroblasts which were co-transfected with human **B7** . It appeared that **B7** could stimulate help for immunoglobulin production much more efficiently than ligation of **CD28** with mAb did. Physical separation of B cells from T cells led to complete abrogation of immunoglobulin production. **Blocking** of CD40 with specific mAb, which have no intrinsic B cell stimulatory properties, or the CD40 ligand with a soluble CD40-human IgM fusion protein, resulted in dose-dependent, but only partial, **inhibition** of T cell-dependent immunoglobulin production with all modes of T cell activation tested. A clear correlation was found between the induction of CD40 ligand expression on the T cells by the **different** modes of co-stimulation and subsequent immunoglobulin production by the B cells. It is concluded that ligation of **CD28** and/or **CTLA-4**, and of CD2 can generate co-stimulatory signals for T cell help for immunoglobulin production, which was found to be only partially dependent on the CD40-CD40 ligand interaction.

15/7/4 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

10710918 EMBASE No: 98144544
Malignant plasma cell lines express a functional **CD28** molecule
Zhang X.-G.; Olive D.; Devos J.; Rebouissou C.; Ghiotto-Ragueneau M.; Ferlin M.; Klein B.
B. Klein, INSERM U475, 99 Rue Puech Ville, 34100 Montpellier cedex France
Leukemia (United Kingdom) , 1998, 12/4 (610-618)
CODEN: LEUKE ISSN: 0887-6924
DOCUMENT TYPE: Journal Article

LANGUAGES: ENGLISH SUMMARY LANGUAGES: ENGLISH
NUMBER OF REFERENCES: 20

The function of **CD28** molecules that are present on malignant plasma cells of human myeloma cell lines (HMCL) was studied. First, myeloma cells expressed a similar density of **CD28** antigen to that of normal T cells. The myeloma **CD28** molecules were able to bind **B7**-Ig molecules as well as L cells transfected with a **B7-1** cDNA, and anti-**CD28** mAb **inhibited** the binding. Myeloma cells did not express **B7-1** antigens but a low density of **B7**-2 antigens. The myeloma **B7**-2 molecules of two HMCL were able to bind **CTLA-4** protein. No autocrine CD28:B7-2 activation could be evidenced as we found no spontaneous binding of the p85 subunit of PI-3 kinase to **CD28** molecules. In addition, a **blocking** anti-**CD28** mAb did not affect the IL-6-dependent or autonomous proliferation of the HMCL. The activation of myeloma **CD28** molecules with or without TPA stimulation did not affect the proliferation, survival, **differentiation** , expression of activation antigens and cytokine receptors or cytokine production of myeloma cells. However, the triggering of myeloma **CD28** molecules by **B7-1** transfectant cells resulted in binding of the p85 subunit of PI-3 kinase to **CD28** molecules as previously shown for T cell **CD28** molecules. This expression of a large density of **CD28** molecules able to bind **B7** molecules might contribute to a downregulation of the immune control of myeloma cells.

15/7/5 (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09570663 98300059
CD4-targeted therapy and **CD28-B7** costimulatory **blockage** may independently induce tolerance in sensitized allograft recipients.
Kato H; Onodera K; Chandraker A; Volk HD; Sayegh MH; Kupiec-Weglinski JW
Harvard Medical School, Department of Surgery and Medicine, Brigham & Women's Hospital, Boston, Massachusetts, USA.
Transplant Proc (UNITED STATES) Jun 1998, 30 (4) p1063-4, ISSN 0041-1345 Journal Code: WE9
Contract/Grant No.: A123847; A134965
Languages: ENGLISH
Document type: JOURNAL ARTICLE

15/7/6 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09560176 98285779
Costimulatory pathways in lymphocyte proliferation induced by the simian immunodeficiency virus SIVsmmPBj14.
Whetter L; Novembre FJ; Saucier M; Gummuluru S; Dewhurst S
Department of Microbiology and Immunology, University of Rochester Medical Center, Rochester, New York 14642, USA.
J Virol (UNITED STATES) Jul 1998, 72 (7) p6155-8, ISSN 0022-538X Journal Code: KCV
Contract/Grant No.: RO1 AI39397, AI, NIAID; KO4 AI01240, AI, NIAID; RO1 CA67364, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The PBj14 isolate of the simian immunodeficiency virus SIVsmmPBj14 is unique among primate lentiviruses in its ability to induce lymphocyte proliferation and acutely lethal disease. The studies reported here show that viral induction of T-cell proliferation requires accessory cells, such as primary monocytes or Raji B-lymphoma cells, as well as the presence of a putative immunoreceptor tyrosine-based activation motif within the viral Nef protein. Addition of CTLA4-immunoglobulin fusion protein or anti-

B7 antibodies to virally infected T cells led to substantial, but not complete, **inhibition** of monocyte-costimulated T-cell proliferation-suggesting that both **CD28/B7**-dependent and non-**CD28** -dependent pathways may contribute to the costimulation of virally induced lymphoproliferation. Finally, cyclosporin A, a specific **inhibitor** of the calcium-calmodulin-regulated phosphatase activity of calcineurin, which influences activation of the transcription factor nuclear factor of activated T cells, was shown to **block** virally mediated T-cell proliferation. Taken together, these findings suggest that the effect of SIVsmmPBj14 on T-cell activation may be functionally analogous, at least in part, to the effect of engagement of the T-cell receptor.

15/7/7 (Item 3 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09479050 98209763
Strength of TCR signal determines the costimulatory requirements for Th1 and Th2 CD4+ T cell differentiation.
Tao X; Constant S; Jorritsma P; Bottomly K
Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06510, USA.
J Immunol (UNITED STATES) Dec 15 1997, 159 (12) p5956-63, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI26791, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Differentiation of naive CD4 T cells into cytokine-secreting effector Th1 and Th2 cells is influenced by several factors. We have previously reported that the affinity of antigen for TCR and antigen dose can influence the differentiation of Th1 and Th2 cells. Several in vitro and in vivo models have demonstrated a role for the costimulatory molecules, **B7-1** (CD80) and **B7** -2 (CD86), in the generation of distinct effector T cell responses. To determine whether the strength of TCR signaling controls the involvement of **CD28** costimulation in selective CD4 T cell differentiation, naive CD4 T cells bearing a transgenic TCR are primed by a weak or strong TCR signal (signal 1) in the presence or absence of **B7** costimulatory molecules (signal 2). In this system, IL-4-producing Th2 cells are generated by priming with a weak but not a strong TCR signal. Th2 cell differentiation is dependent on **CD28/B7** interactions in that disruption of **CD28/B7** interactions **inhibits** the priming of Th2 cells and cross-linking **CD28** with anti-**CD28** **antibody** augments the priming of Th2 cells. In contrast, however, IL-4-producing Th2 cells cannot be generated by priming with a strong TCR signal even in the presence of strong costimulation or high doses of IL-2. Thus, our results suggest that naive CD4 T cells are receptive to **CD28** -dependent IL-4 production only if they receive a weak TCR signal.

15/7/8 (Item 4 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09447280 98168989
Nucleic acid vaccine-induced immune responses require **CD28** costimulation and are regulated by CTLA4.
Horspool JH; Perrin PJ; Woodcock JB; Cox JH; King CL; June CH; Harlan DM; St. Louis DC; Lee KP
Immune Cell Biology Program, Naval Medical Research Institute, Bethesda, MD 20889, USA.
J Immunol (UNITED STATES) Mar 15 1998, 160 (6) p2706-14, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH
Document type: JOURNAL ARTICLE
Immunization with plasmids expressing specific genes (DNA or nucleic acid vaccination (NAV)) elicits robust humoral and cell-mediated immune responses. The mechanisms involved in T cell activation by NAV are incompletely characterized. We have examined the costimulatory requirements of NAV. **CD28** -deficient mice did not mount Ab or CTL responses following i.m. immunization with eukaryotic expression plasmids encoding the bacterial gene beta-galactosidase (beta gal). Because these mice retained their ability to up-regulate the CTLA4 receptor (a negative regulator of T cell activation), we examined CTLA4's role in the response of wild-type BALB/c mice to NAV. Intact anti-CTLA4 mAb but not Fab fragments **suppressed** the primary humoral response to pCIA/beta gal without affecting recall responses, indicating CTLA4 activation **inhibited** Ab production but not T cell priming. **Blockade** of the ligands for **CD28** and CTLA4, CD80 (**B7-1**) and CD86 (**B7**-2), revealed distinct and nonoverlapping function. **Blockade** of CD80 at initial immunization completely abrogated primary and secondary Ab responses, whereas **blockade** of CD86 **suppressed** primary but not secondary responses. Simultaneous **blockade** of CD80 + CD86 was less effective at **suppressing** Ab responses than either alone. Enhancement of costimulation via coinjection of **B7** -expressing plasmids augmented CTL responses but not Ab responses, and without evidence of Th1 to Th2 skewing. These findings suggest complex and distinct roles for **CD28** , CTLA4, CD80, and CD86 in T cell costimulation following nucleic acid vaccination.

15/7/9 (Item 5 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09378849 98084483
Modulation of murine Lyme borreliosis by interruption of the **B7/CD28** T-cell costimulatory pathway.
Shanafelt MC; Kang I; Barthold SW; Bockenstedt LK
Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06520, USA. Linda.Bockenstedt@Yale.edu
Infect Immun (UNITED STATES) Jan 1998, 66 (1) p266-71, ISSN 0019-9567 Journal Code: GO7
Contract/Grant No.: AR 07107, AR, NIAMS; AR 42637, AR, NIAMS; AI 45253, AI, NIAID; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recent studies have implicated cytokines associated with Th2 cells in the genetic resistance to murine Lyme borreliosis. Because the **B7/CD28** costimulatory pathway has been shown to influence the differentiation of Th-cell subsets, we investigated the contribution of the **B7** molecules CD80 and CD86 to the Th2 cytokine profile and development of arthritis in BALB/c mice infected with Borrelia burgdorferi. Effective **blockade** of CD86/**CD28** interaction was demonstrated by elimination of interleukin 4 (IL-4) and upregulation of gamma interferon (IFN-gamma) responses by B. burgdorferi-specific T cells and by reduction of B. burgdorferi-specific immunoglobulin G. Despite the shift toward a Th1 cytokine pattern, which others have associated with disease susceptibility, the severity of arthritis was unchanged. Moreover, combined CD80/CD86 **blockade** by using anti-CD80 and anti-CD86 monoclonal **antibodies** or CTLA-4Ig enhanced IFN-gamma production over that seen with CD86 **blockade** alone, yet augmentation of this Th1-associated cytokine did not enhance disease. These results demonstrate that IL-4 production by T cells in B. burgdorferi-infected BALB/c mice is dependent upon CD86/**CD28** interaction and that this cytokine does not contribute significantly to host resistance to the development of arthritis. In addition, combined CD80/CD86 **blockade** resulted in preferential expansion of IFN-gamma-producing T cells in B. burgdorferi infection,

suggesting that costimulatory pathways other than **B7/CD28** may contribute to T-cell activation during continuous antigen stimulation. These studies may provide insight into the role of the **B7/CD28** pathway in other infectious and autoimmune diseases in which deviation of Th cell immune responses occurs and antigen is persistently present.

15/7/10 (Item 6 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09207121 95378786
Identification of residues in the V domain of CD80 (**B7-1**) implicated in functional interactions with **CD28** and CTLA4.
Fargeas CA; Truneh A; Reddy M; Hurle M; Sweet R; Sekaly RP
Laboratoire d'Immunologie, Institut de Recherches Cliniques de Montreal, Quebec, Canada.
J Exp Med (UNITED STATES) Sep 1 1995, 182 (3) p667-75, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The CD80 (**B7-1**) molecule is a 45-60-kD member of the immunoglobulin superfamily that is expressed on a variety of cell types of haematopoietic origin. CD80 can provide a critical costimulatory signal to T cells by interacting with the T cell surface molecule **CD28**. CD80 also binds to the **CD28**-related molecule CTLA4, which is expressed on activated T cells, Recently, additional ligands of **CD28** and CTLA4 have been described in mice and humans. One of them, CD86 (B-70 or **B7** -2) was characterized at the molecular level. Although similar in predicted structure to CD80, it is distantly related in amino acid sequence. In this study, human CD80 mutants were generated and tested for their ability to maintain the interaction with **CD28** leading to adhesion and enhanced IL-2 production. Two hydrophobic residues in the V-like domain of CD80 were identified as critical for binding to **CD28** and are also important for the interaction with CTLA4. These residues are adjacent to the epitope of the BB1 **antibody**, which **inhibits CD28**-CD80 interactions. One of these residues, Y87, is conserved in all CD80 and CD86 cloned from various species. These results being to unravel the structural requirements for binding to **CD28** and CTLA4.

15/7/11 (Item 7 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09186233 97461424
Long-term **inhibition** of murine lupus by brief simultaneous **blockade** of the **B7/CD28** and CD40/gp39 costimulation pathways.
Daikh DI; Finck BK; Linsley PS; Hollenbaugh D; Wofsy D
Department of Medicine, Department of Veterans Affairs Medical Center, San Francisco, CA 94121, USA. daikh@itsa.ucsf.edu
J Immunol (UNITED STATES) Oct 1 1997, 159 (7) p3104-8, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Murine lupus in NZB/NZW F1 (B/W) mice can be retarded by sustained administration of CTLA4Ig and by brief treatment early in life with mAb that **block** CD40/gp39 interactions. We sought to determine whether brief therapy with CTLA4Ig could provide sustained benefit in B/W mice and whether a synergistic effect could be derived by **blockade** of both the **B7/CD28** and the CD40/gp39 pathways. We found that a short course of CTLA4Ig at the onset of disease produced only short-term benefit. However, when CTLA4Ig was combined with anti-gp39, there was long-lasting **inhibition** of autoantibody production and renal disease. Ten months

after the 2-wk course of therapy, 70% of these mice were alive, compared with only 18% and 0% of those that received only anti-gp39 or CTLA4Ig, respectively. These findings demonstrate that brief simultaneous **blockade** of the **B7/CD28** and CD40/gp39 costimulation pathways can produce benefit that lasts long after treatment has been discontinued.

15/7/12 (Item 8 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09124319 97368326
Manipulation of T cell costimulatory and **inhibitory** signals for immunotherapy of prostate cancer.
Kwon ED; Hurwitz AA; Foster BA; Madias C; Feldhaus AL; Greenberg NM; Burg MB; Allison JP
Laboratory of Kidney and Electrolyte Metabolism, National Heart, Lung, and Blood Institute, National Institutes of Health, Room 1N105, Building 9, 9 Memorial Drive, MSC-0951 Bethesda, MD 20892-0951, USA. kwone@fido.nhlbi.nih.gov
Proc Natl Acad Sci U S A (UNITED STATES) Jul 22 1997, 94 (15) p8099-103, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: CA57986, CA, NCI; CA64851, CA, NCI; CA40041, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The identification of potentially useful immune-based treatments for prostate cancer has been severely constrained by the scarcity of relevant animal research models for this disease. Moreover, some of the most critical mechanisms involved in complete and proper antitumoral T cell activation have only recently been identified for experimental manipulation, namely, components involved in the costimulatory pathway for T cell activation. Thus, we have established a novel syngeneic murine prostate cancer model that permits us to examine two distinct manipulations intended to elicit an antiprostate cancer response through enhanced T cell costimulation: (i) provision of direct costimulation by prostate cancer cells transduced to express the **B7.1** ligand and (ii) in vivo **antibody**-mediated **blockade** of the T cell **CTLA-4**, which prevents T cell down-regulation. In the present study we found that a tumorigenic prostate cancer cell line, TRAMPC1 (pTC1), derived from transgenic mice, is rejected by syngeneic C57BL/6 mice, but not athymic mice, after this cell line is transduced to express the costimulatory ligand **B7.1**. Also, we demonstrated that in vivo **antibody**-mediated **blockade** of **CTLA-4** enhances antiprostate cancer immune responses. The response raised by anti-**CTLA-4** administration ranges from marked reductions in wild-type pTC1 growth to complete rejection of these cells. Collectively, these experiments suggest that appropriate manipulation of T cell costimulatory and **inhibitory** signals may provide a fundamental and highly adaptable basis for prostate cancer immunotherapy. Additionally, the syngeneic murine model that we introduce provides a comprehensive system for further testing of immune-based treatments for prostate cancer.

15/7/13 (Item 9 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09122636 97400338
CD28-B7 T cell costimulatory **blockade** by CTLA4Ig in sensitized rat recipients: induction of transplantation tolerance in association with depressed cell-mediated and humoral immune responses.
Onodera K; Chandraker A; Schaub M; Stadlbauer TH; Korom S; Peach R; Linsley PS; Sayegh MH; Kupiec-Weglinski JW

Department of Surgery, Harvard Medical School, Boston, MA 02115, USA.
J Immunol (UNITED STATES) Aug 15 1997, 159 (4) p1711-7, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: RO1AI23847, AI, NIAID; RO1AI34965, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We tested the effects of **blocking CD28-B7** T cell costimulation by using CTLA4Ig in an established transplantation model in which LBNF1 cardiac allografts are rejected in an accelerated manner (<36 h) by LEW rats presensitized with Brown-Norway skin grafts. Treatment with CTLA4Ig with or without donor alloantigen in the sensitization phase (between skin and cardiac engraftment) minimally delayed accelerated rejection. However, adjunctive infusion of CTLA4Ig and donor alloantigen in the effector phase (after cardiac engraftment) resulted in long term graft survival and donor-specific tolerance in 30 to 50% of the recipients. The mutant form of CTLA4Ig, which **blocks B7-1** but not **B7** -2, was ineffective. The tolerant state was accompanied by reduction of cell-mediated (MLR/CTL) responses and depression of humoral (circulating IgM/IgG allo-Abs) alloreactivity in vivo. Hence, the binding of **CD28** on T cells to both CD80 and CD86 ligands represents a crucial initial costimulatory step leading to accelerated graft rejection. CTLA4Ig-mediated early **blockade** of the **CD28** signaling pathway combined with transfusion of donor cells in the perioperative period interrupts sensitization and may produce transplantation tolerance. This regimen **inhibits** T cell costimulation and activation to provide help to CD8+ cytotoxic T and B cells, perhaps, via CTLA4Ig-induced clonal anergy or deletion.

15/7/14 (Item 10 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09095901 97343407

The IgV domain of human **B7**-2 (CD86) is sufficient to co-stimulate T lymphocytes and induce cytokine secretion.

Rennert P; Furlong K; Jellis C; Greenfield E; Freeman GJ; Ueda Y; Levine B; June CH; Gray GS

Department of Molecular Biology, Repligen Corp., Cambridge, MA 02139, USA.
Int Immunol (ENGLAND) Jun 1997, 9 (6) p805-13, ISSN 0953-8178 Journal Code: AY5
Languages: ENGLISH
Document type: JOURNAL ARTICLE

B7-1 (CD80) and **B7** -2 (CD86) are genetically and structurally related molecules expressed on antigen-presenting cells. Both bind **CD28** to co-stimulate T lymphocytes, resulting in proliferation and cytokine production. The extracellular portions of **B7-1** and **B7**-2 which bind to **CD28** and **CTLA-4** are related to Ig variable (V) and Ig constant (C) domain sequences. Recent reports have described splice variant forms of **B7** proteins which occur in vivo and are of unknown function. Here we describe soluble recombinant forms of **B7-1** and **B7** -2 containing either both of the Ig-like extracellular domains or the individual IgV or IgC domains coupled to an Ig Fc tail. Soluble **B7-1** and **B7**-2 bind to **CD28** and **CTLA-4**, and effectively co-stimulate T lymphocytes resulting in their proliferation and the secretion of cytokines. Furthermore, the IgV domain of **B7**-2 binds **CD28** and **CTLA-4**, competes with **B7-1** and **B7** -2 for binding to these receptors, and co-stimulates T lymphocytes. Cross-linked soluble **B7**-2v was the most potent co-stimulatory molecule tested and was active at a concentration approximately 100-fold lower than cross-linked soluble **B7-1** or **B7**-2 proteins. When bound to tosyl-activated beads, **B7**-2v was capable of sustaining multiple rounds of T cell expansion. These data complement the description of naturally occurring variants to suggest that

T cell co-stimulation in vivo may be regulated by soluble or truncated forms of **B7** proteins.

15/7/15 (Item 11 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09028047 97296320
Costimulation through **B7**-2 (CD86) is required for the induction of a lung mucosal T helper cell 2 (TH2) immune response and altered airway responsiveness.
Tsuyuki S; Tsuyuki J; Einsle K; Kopf M; Coyle AJ
R&D Dept. Kissei Pharmaceutical Co. Ltd., Matsumoto, Japan.
J Exp Med (UNITED STATES) May 5 1997, 185 (9) p1671-9, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The recruitment of eosinophils into the airways after allergen exposure is dependent on interleukin (IL) 5 secreted from antigen-specific CD4+ T cells of the T helper cell (Th) 2 subset. However, while it is established that costimulation through **CD28** is required for TCR-mediated activation and IL-2 production, the importance of this mechanism for the induction of a Th2 immune response is less clear. In the present study, we administered the fusion protein **CTLA-4** immunoglobulin (Ig) into the lungs before allergen provocation to determine whether **CD28**/**CTLA-4** ligands are required for allergen-induced eosinophil accumulation and the production of Th2 cytokines. Administration of **CTLA-4** Ig **inhibited** the recruitment of eosinophils into the lungs by 75% and **suppressed** IgE in the bronchoalveolar lavage fluid. **CTLA-4** Ig also **inhibited** the production of IL-4, IL-5, and IL-10 by 70-80% and enhanced interferon-gamma production from CD3-T cell receptor-activated lung Thy1.2+ cells. Allergen exposure upregulated expression of **B7**-2, but not **B7-1**, on B cells from the lung within 24 h. Moreover, airway administration of an anti-**B7**-2 monoclonal **antibody** (mAb) **inhibited** eosinophil infiltration, IgE production, and Th2 cytokine secretion comparable in magnitude to that observed with **CTLA-4** Ig. Treatment with an anti-**B7-1** mAb had a small, but significant effect on eosinophil accumulation, although was less effective in **inhibiting** Th2 cytokine production. The anti-**B7**-2, but not anti-**B7-1**, mAb also **inhibited** antigen-induced airway hyperresponsiveness in vivo. In all of the parameters assessed, the combination of both the anti-**B7-1** and anti-**B7**-2 mAb was no more effective than anti-**B7**-2 mAb treatment alone. We propose that strategies aimed at **inhibition** of **CD28** interactions with **B7**-2 molecules may represent a novel therapeutic target for the treatment of lung mucosal allergic inflammation.

15/7/16 (Item 12 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09010996 97272122
Effects of **blocking B7-1** and **B7**-2 interactions during a type 2 in vivo immune response.
Greenwald RJ; Lu P; Halvorson MJ; Zhou X; Chen S; Madden KB; Perrin PJ; Morris SC; Finkelman FD; Peach R; Linsley PS; Urban JF Jr; Gause WC
Department of Microbiology, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA.
J Immunol (UNITED STATES) May 1 1997, 158 (9) p4088-96, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI31678, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The costimulatory signal provided to T cells through **CD28/CTLA-4** interactions is required for in vivo Th cell effector function associated with cytokine production. However, it is uncertain whether the two well-characterized ligands for these molecules, **B7-1** and **B7**-2, **differentially** influence the consequent development of a type 1 or a type 2 primary response. We have examined the in vivo effects of **blocking B7-1** and/or **B7**-2 ligand interactions on the type 2 mucosal immune response that follows oral infection of mice with the nematode parasite, Heligmosomoides polygyrus. Administration of the combination of anti-**B7-1** and anti-**B7**-2 Abs **inhibited** H. polygyrus-induced increases in serum IgG1 and IgE levels, the expansion of mesenteric lymph node (MLN) germinal centers, in situ CD4+ T cell expansion, elevated blood eosinophils, and increased intestinal mucosal mast cells. Similarly, both Abs **blocked** MLN and Peyer's patch cytokine gene expression and elevations in MLN T cell-derived IL-4 protein secretion. However, in the same experiments, administration of either anti-**B7-1** or anti-**B7**-2 Abs alone had little effect on any of these parameters. T cell and B cell activation was also **blocked** by the combination of anti-**B7**-2 and a **B7-1** -specific mutant Y100F CTLA-4Ig construct. These results suggest that to the extent that anti-**B7-1** and anti-**B7**-2 mAbs **block B7** interactions, either **B7-1** or **B7**-2 ligand interactions can provide the required costimulatory signals that lead to T cell effector function during a type 2 in vivo immune response.

15/7/17 (Item 13 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08886836 97144626

CD28-B7 T cell costimulatory **blockade** by CTLA4Ig in the rat renal allograft model: **inhibition** of cell-mediated and humoral immune responses in vivo.

Akalin E; Chandraker A; Russell ME; Turka LA; Hancock WW; Sayegh MH
Laboratory of Immunogenetics and Transplantation, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, USA.

Transplantation (UNITED STATES) Dec 27 1996, 62 (12) p1942-5, ISSN 0041-1337 Journal Code: WEJ
Contract/Grant No.: AI33100, AI, NIAID; AI37691, AI, NIAID; AI349965, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Blocking CD28-B7 T-cell costimulation by CTLA4Ig induces tolerance to rat renal allografts and **inhibits** Th1, but spares Th2, cytokines. We now report on the mechanisms of **CD28-B7 blockade** in this model. Lymphocytes from CTLA4Ig-treated animals showed significant reduction of mixed lymphocyte response, as well as antidonor cytotoxic T-cell effector function, as compared with rejecting controls. Flow cytometry studies on sera of renal allograft recipients showed complete **inhibition** of antidonor humoral responses by CTLA4Ig. Analysis by reverse transcriptase-polymerase chain reaction and immunohistology showed that intragraft macrophage products, monocyte chemoattractant protein-1 and inducible nitric oxide synthase, were reduced by CTLA4Ig therapy. Immunohistologic studies also showed reduced intragraft macrophage infiltration and decreased staining for the fibrogenic and mitogenic growth factor, transforming growth factor-beta. These results indicate that **CD28-B7 blockade inhibits** cell-mediated and humoral immune responses, and suggest that strategies targeting T-cell costimulation may provide a novel approach to prevent chronic allograft rejection.

15/7/18 (Item 14 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08884221 97149446
CD80 costimulation is essential for the induction of airway eosinophilia.
Harris N; Peach R; Naemura J; Linsley PS; Le Gros G; Ronchese F
Malaghan Institute of Medical Research, Wellington School of Medicine, New Zealand.
J Exp Med (UNITED STATES) Jan 6 1997, 185 (1) p177-82, ISSN 0022-1007 Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CD80 and CD86 (**B7-1** and **B7** -2) are the ligands on antigen-presenting cells (APCs) which bind **CD28** and deliver the costimulatory signals necessary for T cell activation. The reasons for the existence of two **CD28** binding molecules are not well understood. We created a mutant version of CTLA4-Ig that could selectively bind CD80 and **block** **CD28**-CD80 interaction but leave **CD28**-CD86 binding intact. CD80 **blockade** prevented antigen-induced accumulation of eosinophils and lymphocytes in the lung of immunized mice, but did not **block** antigen induced systemic blood eosinophilia or IgE **antibody** production. No preferential expression of CD80 could be demonstrated on a population of lung APC consisting mainly of macrophages. These results indicate that CD80 costimulation is not necessary for the induction of Th2 immune responses but rather for the maintenance or amplification of lung inflammatory responses.

15/7/19 (Item 15 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08820463 97098700
Regulation of surface and intracellular expression of CTLA4 on mouse T cells.
Alegre ML; Noel PJ; Eisfelder BJ; Chuang E; Clark MR; Reiner SL; Thompson CB
Howard Hughes Medical Institute, Gwen Knapp Center for Lupus and Immunology Research, University of Chicago, IL 60637, USA.
J Immunol (UNITED STATES) Dec 1 1996, 157 (11) p4762-70, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: PO1AI35294, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CTLA4 is a cell surface molecule that shares 30% homology with **CD28** and binds **B7** family members with high affinity. Analysis of surface expression on murine T cells revealed up-regulation after stimulation with anti-CD3 mAb in vitro and further augmentation after the addition of exogenous IL-2 or anti-**CD28** mAb. The effects of IL-2 and anti-**CD28** mAb were additive and in part independent, as anti-**CD28** mAb increased anti-CD3 mAb-induced T cell CTLA4 expression in IL-2-deficient mice. In contrast, CTLA4 expression was only minimally augmented by the addition of IL-4, IL-6, IL-7, or IL-12. Expression of CTLA4 induced by anti-CD3 mAb was **inhibited** by anti-IL-2 plus anti-IL-2R mAbs. Inasmuch as these agents prevented T cell proliferation, the effects of cell cycle **inhibitors** also were examined. Drugs **blocking** at G1 (cyclosporin A, mimosine) or S (hydroxyurea) phase **inhibited** the up-regulation of CTLA4 induced by anti-CD3 mAb, suggesting that entry into the cell cycle was necessary to increase the expression of CTLA4. The kinetics of intracellular expression of CTLA4 after stimulation with anti-CD3 mAb paralleled those of surface expression, but surprisingly, much more CTLA4 was localized in the cytoplasm of T lymphocytes than on the cell surface at each time point. Importantly, surface CTLA4 was rapidly internalized intracellularly, which may explain the low levels of expression generally detected on the cell surface. We conclude that both **CD28** and IL-2 play important roles in the

up-regulation of CTLA4 expression. In addition, the cell surface accumulation of CTL4 appears to be primarily regulated by its rapid endocytosis.

15/7/20 (Item 16 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08806566 97032622
Blockade of multiple costimulatory receptors induces hyporesponsiveness: **inhibition** of CD2 plus **CD28** pathways.
Woodward JE; Qin L; Chavin KD; Lin J; Tono T; Ding Y; Linsley PS; Bromberg JS; Baliga P
Department of Microbiology and Immunology, Medical University of South Carolina, Charleston 29425, USA.
Transplantation (UNITED STATES) Oct 15 1996, 62 (7) p1011-8, ISSN 0041-1337 Journal Code: WEJ
Contract/Grant No.: AI 32655, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
T-lymphocyte activation requires engagement of the T cell receptor with antigen-major histocompatibility complex, and simultaneous ligation of costimulatory pathways via the lymphocyte receptors CD2 and **CD28**/CTLA4. Anti-CD2 monoclonal **antibody** (mAb) **blocks** the interaction of the antigen-presenting cell receptor CD48 with its ligand CD2, whereas CTLA4Ig binds with high affinity to the antigen-presenting cell ligands **B7-1** and **B7**-2, **blocking** their interaction with **CD28**/CTLA4. We tested the immunosuppressive effects of simultaneously **blocking** both costimulatory pathways. Using donor C57BL/6J (H2b) hearts transplanted to CBA/J (H2k) recipients, anti-CD2 mAb plus CTLA4Ig administered at the time of transplantation prolonged cardiac allograft mean survival time to >120 days compared with untreated controls (12.2+/-0.5 days, P<0.01), anti-CD2 mAb alone (24.8+/-1.0 days, P<0.01), or CTLA4Ig alone (55.0+/-2.0 days, P<0.01). Retransplantation of these recipients with donor-specific and third-party grafts demonstrated that hyporesponsiveness and tolerance were achieved. In vitro stimulation of lymphocytes from tolerant recipients with donor-specific alloantigen resulted in normal cytotoxic T lymphocyte and mixed lymphocyte reaction responses, showing that clonal deletion or anergy did not occur, but that graft adaptation or **suppression** likely helped to maintain long-term graft survival. In vitro combinations of anti-CD2 mAb and CTLA4Ig **suppressed** the generation of allogeneic cytotoxic T lymphocytes (58%) and the mixed lymphocyte reaction (36%); CTLA4Ig was more effective in this regard and the two agents were not synergistic. Anti-CD2 mAb and CTLA4Ig **suppressed** mitogen-driven proliferation in differential fashions, suggesting that they affected independent signaling pathways. Anti-CD2 mAb and CTLA4Ig also **inhibited** interleukin (IL)-2, IL-4, and IL-2 receptor (CD25). These data indicate that anti-CD2 mAb plus CTLA4Ig induces hyporesponsiveness and tolerance. The mechanism is likely related to the initial disruption of independent pathways of T-lymphocyte activation leading to antigen-specific long-term graft survival.

15/7/21 (Item 17 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08782571 97086728
H. polygyrus: **B7**-independence of the secondary type 2 response.
Gause WC; Lu P; Zhou XD; Chen SJ; Madden KB; Morris SC; Linsley PS; Finkelman FD; Urban JF
Department of Microbiology and Immunology, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814, USA.
Exp Parasitol (UNITED STATES) Nov 1996, 84 (2) p264-73, ISSN

0014-4894 Journal Code: EQP
Contract/Grant No.: AI 21328, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The gastrointestinal nematode parasite, Heligmosomoides polygyrus, has been used extensively in experimental studies of host immunity. The pronounced type 2 primary immune response to H. polygyrus is associated with elevated CD4+, TCR-alpha/beta + T cell IL-4 production and elevated serum IgE levels that are **blocked** by **inhibiting CD28/** CTLA4-**B7** interactions following in vivo administration of the chimeric fusion protein, CTLA4Ig. In the present study, we have examined the in vivo effects of **blocking** CTLA4Ig ligands on the secondary type 2 mucosal host protective immune response to this parasite. Our results show that although CD4+, TCR-alpha/beta + cells remain the primary source of elevated IL-4 during the secondary response, the protective immune response and the effector cell activity associated with it is **B7** -independent as CTLA4Ig administration at the time of challenge does not **block** (1) elevations in T cell IL-4 gene expression or protein secretion; (2) elevations in serum IgE levels, mucosal mastocytosis, or eosinophilia; or (3) host protection, as measured by adult worm burden and fecundity. These findings suggest that memory T helper cells do not require **CD28-B7** interactions for their activation to effector cells that can mediate a host protective type 2 immune response.

15/7/22 (Item 18 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08782277 97054643

Prevention and amelioration of collagen-induced arthritis by **blockade** of the **CD28** co-stimulatory pathway: requirement for both **B7-1** and **B7**-2.

Webb LM; Walmsley MJ; Feldmann M
Kennedy Institute of Rheumatology, Sunley Division, London, GB.

Eur J Immunol (GERMANY) Oct 1996, 26 (10) p2320-8, ISSN 0014-2980 Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Collagen type II-induced arthritis (CIA) is an experimental model of arthritis that has been successfully used to dissect the pathogenesis of human rheumatoid arthritis and to identify potential therapeutic targets. We have used this model to evaluate the role of T cell co-stimulation in both disease development and progression. T cell co-stimulation is provided by ligation of **CD28** with either **B7-1** or **B7**-2 present on antigen-presenting cells and can be prevented by a soluble form of **CTLA-4** (CTLA-4Ig) which binds with high affinity to both **B7-1** and **B7**-2. We found that administration of CTLA-4Ig at the time of immunization prevented the development of CIA and was associated with lack of lymphocyte expansion within the draining lymph node and failure to produce anti-collagen IgG1 or IgG2a **antibodies**. To determine which **CD28** ligand plays a more dominant role in CIA, we treated mice with monoclonal **antibodies** (mAb) against either **B7** -1 or **B7**-2. Neither anti-**B7-1** nor anti-**B7**-2 had any effect on the course of CIA when given alone, but resulted in reduced incidence and clinical scores when given together. Interestingly, when treatment was delayed until after the onset of clinical disease, both CTLA-4Ig or anti-**B7-1** plus anti-**B7** -2 mAb still ameliorated disease. Effective treatment was associated with a reduction in interferon-gamma production by lymph node cells following stimulation in vitro, suggesting that Th1 responses were diminished. This study points to a critical role of **CD28** co-stimulation in the development and perpetuation of CIA in DBA/1 mice. Interestingly, it demonstrates an active role for T cells in the later stages of this disease and implicates both **B7-1** and **B7**-2-mediated co-stimulation in the pathogenesis

of CIA.

15/7/23 (Item 19 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08730874 96298734
Superantigen responses and co-stimulation: **CD28** and **CTLA-4** have opposing effects on T cell expansion in vitro and in vivo.
Krummel MF; Sullivan TJ; Allison JP
Department of Molecular and Cell Biology, University of California, Berkeley 94720, USA.
Int Immunol (ENGLAND) Apr 1996, 8 (4) p519-23, ISSN 0953-8178 Journal Code: AY5
Contract/Grant No.: CA40041, CA, NCI; CA09179, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Co-stimulation via the **CD28/CTLA-4** system appears critical for T cell proliferation to peptide antigens presented in association with MHC. In this study, we examine the roles of **CD28** and **CTLA-4** in the response of murine T cells to the superantigen staphylococcal enterotoxin B (SEB). In vitro, **antibodies** against **B7-1/B7**-2 or Fab fragments of anti-**CD28 antibodies** significantly **inhibit** the response of splenocytes to SEB. Conversely, Fab fragments of anti-**CTLA-4 antibodies** augment the proliferative response. Further, addition of **blocking antibodies** directed against **B7-1/B7** -2 augment proliferation co-stimulated by intact anti-**CD28 antibodies**. These data support the hypothesis that **CD28** and **CTLA-4** exert opposing effects upon early T cell activation. In vivo, intact anti-**CD28 antibodies** and non-stimulatory Fab fragments of anti-**CD28** appear to have similar **inhibitory** effects upon the expansion of V beta 8+ T cells. In contrast, both intact and Fab fragments of anti-**CTLA-4** appear to amplify this expansion. We conclude that the SEB response is significantly augmented by **CD28**-derived signaling and this in turn may be attenuated by signals through **CTLA-4**.

15/7/24 (Item 20 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08722180 96179677
Enhancement of antitumor immunity by **CTLA-4 blockade** [see comments]
Leach DR; Krummel MF; Allison JP
Cancer Research Laboratory, University of California, Berkeley, CA 94720, USA.
Science (UNITED STATES) Mar 22 1996, 271 (5256) p1734-6, ISSN 0036-8075 Journal Code: UJ7
Contract/Grant No.: CA57986, CA, NCI; CA09179, CA, NCI; CA40041, CA, NCI
Comment in Science 1996 Mar 22;271(5256):1691
Languages: ENGLISH
Document type: JOURNAL ARTICLE
One reason for the poor immunogenicity of many tumors may be that they cannot provide signals for **CD28**-mediated costimulation necessary to fully activate T cells. It has recently become apparent that **CTLA-4**, a second counterreceptor for the **B7** family of costimulatory molecules, is a negative regulator of T cell activation. Here, in vivo administration of **antibodies** to **CTLA-4** resulted in the rejection of tumors, including preestablished tumors. Furthermore, this rejection resulted in immunity to a secondary exposure to tumor cells. These results suggest that **blockade** of the **inhibitory** effects

of **CTLA-4** can allow for, and potentiate, effective immune responses against tumor cells.

15/7/25 (Item 21 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08693696 96404501
CD28/B7 regulation of Th1 and Th2 subsets in the development of autoimmune diabetes [published erratum appears in Immunity 1997 Feb;6(2):following 215]
Lenschow DJ; Herold KC; Rhee L; Patel B; Koons A; Qin HY; Fuchs E; Singh B; Thompson CB; Bluestone JA
Ben May Institute for Cancer Research, Department of Pathology, University of Chicago, Illinois 60637, USA.
Immunity (UNITED STATES) Sep 1996, 5 (3) p285-93, ISSN 1074-7613
Journal Code: CCF
Contract/Grant No.: GM07183-19, GM, NIGMS; PO1 DK49799, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CD28 ligation delivers a costimulatory signal important in T cell activation. This study demonstrates that the disruption of the **CD28/B7** pathway early in the nonobese diabetic mouse strain, using **CD28** -/- and CTLA41g transgenic mice, promoted the development and progression of spontaneous autoimmune diabetes. Functional analyses of T cells isolated from **CD28** -deficient mice demonstrated that the GAD-specific T cells produced enhanced Th1-type cytokines (IL-2 and IFN gamma) and diminished Th2-type cytokine, IL-4. Moreover, there was a significant decrease in serum levels of anti-GAD **antibodies** of the IgG1 isotype consistent with a profound **suppression** of Th2-type responses in these animals. Thus, the early differentiation of naive diabetogenic T cells into the Th2 subset is dependent upon **CD28** signaling and extends our understanding of the importance of Th1/Th2 balance in the regulation of this spontaneous autoimmune disease.

15/7/26 (Item 22 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08671404 96350343
Long-term survival of rat to mouse cardiac xenografts with prolonged **blockade** of **CD28-B7** interaction combined with peritransplant T-cell depletion.
Rehman A; Tu Y; Arima T; Linsley PS; Flye MW
Department of Surgery, Washington University School of Medicine, St. Louis, Mo. USA.
Surgery (UNITED STATES) Aug 1996, 120 (2) p205-12, ISSN 0039-6060
Journal Code: VC3
Contract/Grant No.: RO1 AI28480, AI, NIAID; PO1 AI3512, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: The hCTLA4Ig/mCTLA4Ig fusion protein of the extracellular domain of human/mouse CTLA4 and the Fc portion of the human/mouse immunoglobulin G1 **block** the **CD28/B7** costimulatory T-cell activation pathway. We evaluated the effect of prolonged **B7-CD28 blockade** , T-cell depletion, or both on rat to mouse cardiac xenografts. METHODS: C57BL/6 (H-2b) mice receiving infant Wistar Furth (RT1u) rat cardiac xenografts were treated with anti-CD4 (GK1.5) and anti-CD8 (2.43) monoclonal **antibodies** (mAb; 0.2 mg intravenous each) on days -2 and 0, hCTLA4Ig or mCTLA4Ig every other day from day 0 until day 14 and then twice a week until day 50 or day 100, or both. Changes in cellular reactivity were assayed by mixed lymphocyte culture and cell-mediated cytotoxicity and the development of cytotoxic

antibodies was serially measured after transplantation. RESULTS: Either human CTLA4Ig or murine CTLA4Ig alone led to significant prolongation of rat to mouse cardiac xenografts (median survival time [MST], 22 or 26 days, respectively [p = 0.008], versus control). hCTLA4Ig given for 50 days in combination with two doses of anti-CD4/CD8 monoclonal **antibodies** further prolonged graft survival (MST, 61 days; p versus control < 0.0001). In this combination, when hCTLA4Ig was continued until day 100, the graft survival was further prolonged (MST, 119 days). mCTLA4Ig for 100 days plus anti-CD4/CD8 similarly prolonged rat xenograft survival (MST, 94 days). However, all cardiac xenografts eventually failed, primarily from humoral rejection. Cytotoxic **antibody** titers rose rapidly only in animals rejecting a graft, and **suppressed** cell-mediated immunity had completely recovered in rejecting recipients. CONCLUSIONS: **Blockage** of the **CD28-B7** costimulatory interaction can **inhibit** both humoral and cell-mediated immune responses and result in the prolonged acceptance of rat to mouse cardiac xenografts. Longer administration of CTLA4Ig and anti-CD4/CD8 monoclonal **antibodies** further prolongs but does not achieve indefinite survival of rat cardiac xenografts.

15/7/27 (Item 23 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08652285 96274097
Role of **B7** signaling in the differentiation of naive CD4+ T cells to effector interleukin-4-producing T helper cells.
Gause WC; Urban JF; Linsley P; Lu P
Department of Microbiology, Uniformed Services University of the Health Sciences, Bethesda, Md. 20814, USA.
Immunol Res (UNITED STATES) 1995, 14 (3) p176-88, ISSN 0257-277X Journal Code: IMR
Contract/Grant No.: RO73AY; A121328
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Signaling through the T cell receptor must be accompanied by costimulatory signals for the differentiation of naive T cells to cytokine-producing effector T helper cells. The costimulatory signal through **CD28** is required for T cell activation resulting in increased interleukin (IL)-2 production in vitro, but its role in the production of IL-4 and in the in vivo response is still unclear. We have examined the effects of **blocking CTLA-4** (the **CD28** homologue) ligand interactions on the in vivo development of IL-4-producing T helper effector cells during a primary mucosal immune response to the nematode parasite Heligmosomoides polygyrus and during a primary systemic immune response to immunogenic anti-IgD **antibodies**. Our results demonstrate that **CD28** and/or **CTLA-4** signaling is required for T cell priming leading to IL-4 cytokine production, B cell activation, and IgE secretion during both immune responses, suggesting that other signaling molecules do not substitute for these molecules in either of these two different immune responses. Furthermore, the **CD28** ligands, **B7-1** and **B7** -2, can substitute for each other in providing the required T cell costimulatory ligand interactions during the primary immune response to H. polygyrus. In contrast, memory T cells during the challenge immune response do not require **CD28/CTLA-4** ligand interactions for IL-4 production and T helper effector function. (84 Refs.)

15/7/28 (Item 24 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08652145 96322716

CTLA-4 blockade enhances clinical disease and cytokine production during experimental allergic encephalomyelitis.

Perrin PJ; Maldonado JH; Davis TA; June CH; Racke MK

Immune Cell Biology Program, Naval Medical Research Institute, Bethesda, MD 20889-5607, USA. rinOpjp@bumed30.med.navy.mil

J Immunol (UNITED STATES) Aug 15 1996, 157 (4) p1333-6, ISSN 0022-1767 Journal Code: IFB

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The **B7** family of cell surface molecules expressed on APC provides accessory signals to T cells via either **CD28** or **CTLA-4**. However, while **CD28** transduces a costimulatory signal that is required for an optimal immune response, **CTLA-4** transmits a negative signal. These studies use an anti-**CTLA-4** mAb to directly address the role of this T cell surface molecule in experimental allergic encephalomyelitis (EAE). **CTLA-4** regulation of disease was assessed during initial immune cell interactions and during the effector stage of the encephalitogenic immune response. The effects of anti-**CTLA-4** treatment were schedule dependent. **CTLA-4 blockade** during the onset of clinical symptoms markedly exacerbated disease, enhancing mortality. Disease exacerbation was associated with enhanced production of the encephalitogenic cytokines TNF-alpha, IFN-gamma and IL-2. Hence, **CTLA-4** regulates the intensity of the autoimmune response in EAE, attenuating inflammatory cytokine production and clinical disease manifestations.

15/7/29 (Item 25 from file: 154)

DIALOG(R)File 154:MEDLINE(R)

08639508 96320229

Expression and function of CD80 and CD86 costimulator molecules on synovial dendritic cells in chronic arthritis.

Summers KL; O'Donnell JL; Williams LA; Hart DN

Christchurch Hospital, New Zealand.

Arthritis Rheum (UNITED STATES) Aug 1996, 39 (8) p1287-91, ISSN 0004-3591 Journal Code: 90M

Languages: ENGLISH

Document type: JOURNAL ARTICLE

OBJECTIVE. To examine CD86 expression on dendritic cells isolated from the synovial fluid (SFDC) of patients with chronic arthritis, and to determine the importance of both CD80 and CD86 molecules in SFDC-T lymphocyte interactions. METHODS. CD86 messenger RNA (mRNA) and surface expression were analyzed in SFDC using reverse transcriptase-polymerase chain reaction and flow cytometry, respectively. The costimulator activity of the SFDC CD80 and CD86 molecules was determined by allogeneic mixed lymphocyte reaction (MLR). CD80 and CD86 induction on SFDC during in vitro culture was also examined. RESULTS. Fresh SFDC either lacked or showed very weak surface expression of CD86 molecules (as shown previously for CD80), yet contained CD86 mRNA. CD80 **antibodies** minimally **inhibited** an allogeneic MLR, whereas CD86 **antibodies** and **CTLA-4** Ig showed significant **inhibition** . Both CD80 and CD86 molecules were inconsistently induced on SFDC following culture in either media, interferon-gamma, or granulocyte-macrophage colony-stimulating factor. CONCLUSION. SFDC may be defective antigen-presenting cells in vivo. The ability of CD80 and CD86 molecules to be induced and become functional on SFDC in vitro implies the presence of a negative regulatory compound(s) in the synovial environment.

15/7/30 (Item 26 from file: 154)

DIALOG(R)File 154:MEDLINE(R)

08635887 96245981
Expression of both **B7-1** and **CD28** contributes to the IL-2 responsiveness of CTLL-2 cells.
Belani R; Weiner GJ
University of Iowa, Iowa City, 52242, USA.
Immunology (ENGLAND) Feb 1996, 87 (2) p271-4, ISSN 0019-2805
Journal Code: GH7
Contract/Grant No.: CA55178, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The CTLL-2 bioassay is used frequently to determine interleukin-2 (IL-2) concentrations in experimental samples, including samples that contain reagents which affect the **CD28-B7** interaction. We therefore evaluated whether the **CD28-B7** pathway plays a role in the growth of CTLL-2 cells. Flow cytometry demonstrated that CTLL-2 cells express both **CD28** and **B7-1** . CTLA4-immunoglobulin (CTLA4-Ig) **inhibited** the growth of CTLL-2 cells over a range of IL-2 concentrations, suggesting that the **CD28-B7** interaction plays an important role in the growth of CTLL-2 cells. Anti-**B7-1** **antibody** also **inhibited** CTLL-2 proliferation at all concentrations of IL-2. These results indicate that the CTLL-2 bioassay may not be a reliable means of determining IL-2 levels in experimental samples containing reagents that affect the **CD28-B7** interaction. They also suggest that co-expression of **CD28** and **B7** may contribute to the growth of malignant T cells.

15/7/31 (Item 27 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08619828 96252071
Costimulation and its role in organ transplantation.
Bluestone JA
Ben May Institute, University of Chicago, IL 60637-1470, USA.
Clin Transplant (DENMARK) Feb 1996, 10 (1 Pt 2) p104-9, ISSN 0902-0063 Journal Code: BB5
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Antigen-specific T-cell activation depends initially on the interaction of the T-cell receptor with peptide/major histocompatibility complex (MHC). In addition, a costimulatory signal, mediated by distinct cell surface accessory molecules such as **CD28**, is required for complete T-cell activation. One essential element of the **CD28** costimulatory system that makes it an attractive target for immunotherapy is the selective effect of **CD28** antagonists on activated T cells. Only cells encountering antigen presenting cells (APCs) without the appropriate **CD28** ligand will be rendered functionally inactive as desired for any next-generation immuno-**suppressive** drug. This brief review will focus on the role of **CD28/B7** interactions in regulating organ graft rejection. In vitro and in vivo studies will describe the use of a soluble fusion protein antagonist of **CD28/B7** (CTLA-4Ig), anti-**B7** MAbs, and genetically altered **CD28** "knockout" mice to study immune responses. The studies suggest that: 1) CTLA-4Ig induces long-term, antigen-specific unresponsiveness in vivo; 2) two distinct ligands for **CD28**, **B7-1** and **B7**-2, are differentially regulated during immune responses; and 3) both **B7-1** and **B7**-2 costimulatory molecules are active, in vivo, although **B7**-2 plays a clearly dominant role in murine allograft rejection. (23 Refs.)

15/7/32 (Item 28 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08616474 96281905

CTLA-4 engagement **inhibits** IL-2 accumulation and cell cycle progression upon activation of resting T cells.

Krummel MF; Allison JP

Department of Molecular and Cell Biology, University of California, Berkeley 94720, USA.

J Exp Med (UNITED STATES) Jun 1 1996, 183 (6) p2533-40, ISSN 0022-1007 Journal Code: I2V

Contract/Grant No.: CA40041, CA, NCI; CA09179, CA, NCI

Languages: ENGLISH

Document type: JOURNAL ARTICLE

While interactions between **CD28** and members of the **B7** family costimulate and enhance T cell responses, recent evidence indicates that the **CD28** homologue **CTLA-4** plays a downregulatory role. The mechanism by which this occurs is not clear, but it has been suggested that **CTLA-4** terminates ongoing responses of activated T cells, perhaps by induction of apoptosis. Here we demonstrate that **CTLA-4** engagement by **antibody** cross-linking or binding to **B7** **inhibits** proliferation and accumulation of the primary T cell growth factor, IL-2, by cells stimulated with anti-CD3 and anti-**CD28**. This **inhibition** is not a result of enhanced cell death. Rather it appears to result from restriction of transition from the G1 to the S phase of the cell cycle. Our observation that upregulation of both the IL-2R alpha chain and the CD69 activation antigen are **inhibited** by **CTLA-4** engagement supplies further evidence that **CTLA-4** restricts the progression of T cells to an activated state. Together this data demonstrates that **CTLA-4** can regulate T cell activation in the absence of induction of apoptotic cell death.

15/7/33 (Item 29 from file: 154)

DIALOG(R)File 154:MEDLINE(R)

08596024 96257796

Human dendritic cells activate T lymphocytes via a CD40: CD40 ligand-dependent pathway.

McLellan AD; Sorg RV; Williams LA; Hart DN

Haematology/Immunology Research Group, Christchurch Hospital and Christchurch School of Medicine, New Zealand.

Eur J Immunol (GERMANY) Jun 1996, 26 (6) p1204-10, ISSN 0014-2980 Journal Code: EN5

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The CD40:CD40 ligand (CD40L) interaction provides T lymphocyte-mediated help for B lymphocyte and monocyte function but has also been shown to serve as a co-stimulus for T lymphocyte activation. In this report, we studied the regulation of CD40 expression and its functional relevance for the human dendritic cell (DC) stimulation of T lymphocytes. Only a small subpopulation of directly isolated blood DC expressed CD40. However, CD40 was rapidly up-regulated by culture, and its expression was further enhanced by interleukin (IL)-1 alpha, IL-1 beta, IL-3, tumor necrosis factor-alpha and granulocyte/macrophage-colony-stimulating factor. Expression of CD40L on DC was not detected. The proliferation of T lymphocytes in an allogeneic mixed leukocyte reaction, stimulated by blood DC or epidermal Langerhans cells, was significantly reduced in the presence of the CD40 immunoglobulin (CD40Ig) fusion protein or CD40L monoclonal **antibodies** . Cross-linking of CD40 on directly isolated DC with mouse CD40L trimer (mCD40LT) markedly augmented CD80 and CD86 up-regulation. Nevertheless, the same cross-linking mCD40LT **inhibited** DC stimulated T lymphocyte proliferation. When CD40Ig was added simultaneously with CTLA-4Ig, only minimal and variable additional **inhibition** of DC-stimulated allogeneic T lymphocyte proliferation and IL-2 secretion was observed, compared to each fusion protein alone. These results suggest that both CD80/CD86-dependent and -independent components of DC-T lymphocyte

CD40:CD40L co-stimulation exist and further emphasize that the majority of blood DC have to differentiate or be activated to express co-stimulatory molecules.

15/7/34 (Item 30 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08591864 96235034
Influence of antigen dose and costimulation on the primary response of CD8+ T cells in vitro.
Cai Z; Sprent J
Department of Immunology, Scripps Research Institute, La Jolla, California 92037, USA.
J Exp Med (UNITED STATES) May 1 1996, 183 (5) p2247-57, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: AI-32068, AI, NIAID; CA-25803, CA, NCI; CA-38355, CA, NCI; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The influence of costimulation on the primary response of CD8+ T cells to class I alloantigens was studied with the aid of a T cell receptor transgenic model and defined peptides as antigen. With small doses of antigen, the proliferative response of CD8+ cells was high early in culture but was of brief duration and declined to low levels by day 4; this abbreviated response was associated with limited production of interleukin 2 (IL-2) and was strongly dependent upon costimulation via CD8-major histocompatibility complex class I and **CD28-B7** interactions.
The response to large doses of antigen was quite different in two respects. First, large doses of antigen **inhibited** the early (day 3) proliferative response but caused a marked elevation of the response late in culture (day 5); these altered kinetics were associated with increased production of IL-2. Second, the initial proliferative response to large doses of antigen did not require costimulation: indeed, **blocking** costimulation with CTLA41g or anti-CD8 monoclonal **antibody** enhanced the early proliferative response. However, **blocking** costimulation impaired IL-2 production and prevented the late proliferative response. These findings indicate that the requirement for costimulation of T cells can be partly overcome by increasing the dose of antigen to a high level. However, costimulation plays a key role in prolonging the response, presumably by triggering strong and sustained production of IL-2.

15/7/35 (Item 31 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08558727 96179497
T-Cell co-stimulation by the **CD28** ligand **B7** is involved in the immune response leading to rejection of a spontaneously regressive tumor.
Chaux P; Martin MS; Martin F
Department of Biology and Therapy of Cancer, Faculty of Medicine, INSERM, Dijon, France.
Int J Cancer (UNITED STATES) Apr 10 1996, 66 (2) p244-8, ISSN 0020-7136 Journal Code: GQU
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cell variants from experimental tumors may lose their tumorigenicity or give rise to tumors that regress after a short period of progression in immunocompetent syngeneic animals. Rejection of these tumor cells is often T-cell-dependent. It has recently been reported that, besides the specific signal delivered through the clonogenic receptor, T-cell activation requires a co-stimulatory signal, delivered through its **CD28** receptor

by **B7-1** and/or **B7**-2 molecules expressed at the surface of the antigen-presenting cells. CTLA4Ig, a fusion molecule that specifically **inhibits** **B7-1** and **B7**-2 binding to their receptors of T cells, was used to investigate the role of **B7** in the spontaneous regression of the tumors induced in syngeneic rats by REGb cells, a regressor cell line established from a chemically induced colon carcinoma. When rats received either 1 or 3 CTLA4Ig injections, REGb tumors grew 3 or 7 times larger than in control animals, respectively. However, in most animals, single or repeated CTLA4Ig injections delayed rather than **suppressed** REGb tumor rejection. **Antibodies** to CTLA4Ig appeared in treated rats and could explain this transient effect. Neither REGb cells nor freshly isolated MHC class-II+ antigen-presenting cells infiltrating REGb tumors expressed **B7**, establishing that the target of CTLA4Ig was not located inside the tumor. In contrast, MHC class-II+ **B7**+ accessory cells were found in the tissue, rather than the tumor itself, was the site of tumor-antigen presentation to tumor-specific T cells. These results establish the role of **B7**/**CD28** co-stimulation pathway in the control of a spontaneously regressive tumor.

15/7/36 (Item 32 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08535326 96153660
Effect of CD80 and CD86 on T cell cytokine production.
Petro TM; Chen SS; Panther RB
Dept. of Oral Biology, University of Nebraska Medical Center, Lincoln, USA.
Immunol Invest (UNITED STATES) Nov 1995, 24 (6) p965-76, ISSN 0882-0139 Journal Code: GI5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Conjugation of the T cell receptor (TCR) with antigen/MHC proteins must be accompanied by conjugation of T cell counterreceptors (**CD28** or **CTLA-4**) with costimulatory molecules CD80 or CD86 (**B7-1** or **B7** -2) on antigen presenting cells (APC) to avert T cell anergy, and to provide essential signals for T cell activation and cytokine production. However, T cells and APC express changing patterns of counterreceptors and costimulatory molecules during the immune response. To determine the involvement of CD80 and CD86 in costimulation of T cell cytokine production, T cells were incubated with peritoneal exudate macrophages, which express CD80 and CD86, and stimulated in vitro for 48 or 72 hrs with anti-CD3 in the presence or absence of **blocking antibody** to CD80 or CD86. Alternatively, enriched anti-CD3 stimulated T cells were costimulated with **antibody** to **CD28** and **CTLA-4** . Production of T cell IL-2, IL-4, and IL-5 was depressed in the presence of anti-CD86 but not anti-CD80. Production of IFN-gamma was significantly **blocked** by either anti-CD80 and anti-CD86. Anti-**CD28** was a potent costimulator of IFN-gamma and IL-2 production, but a less potent costimulator of IL-4 and IL-5 production. The data suggest that T cell counterreceptors and APC costimulatory molecules act with varying efficacies at stimulating production of T cell cytokines.

15/7/37 (Item 33 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08492592 96036900
Cell-cell interactions regulate dendritic cell-dependent HIV-1 production in CD4+ T lymphocytes.
Pinchuk LM; Polacino PS; Agy MB; Klaus SJ; Clark EA
Regional Primate Research Center, University of Washington Medical Center, Seattle 98195, USA.

Adv Exp Med Biol (UNITED STATES) 1995, 378 p461-3, ISSN 0065-2598
Journal Code: 2LU
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We investigated the role of blood dendritic cells (DC) in transmission of HIV-1 from infected to uninfected CD4+ T cells, and the accessory molecules involved. DC promoted transmission from infected to uninfected CD4+ cells, but blood DC themselves were not infectable. DC-mediated transmission was **blocked** by mAb to CD4 and MHC class II, but strongly increased by mAb to CD40 on DC or **CD28** on T cells. The DC-dependent infection was **inhibitable** by anti-CD80 and a soluble fusion protein of the CD80 ligand, CTLA4; soluble CTLA4Ig also **blocked** infection augmented by crosslinking CD40. We also demonstrated that mAb to CD40 up-regulate the expression of CTLA4 ligands CD80 and B70/**B7**-2 (CD86) on DC. These data suggest that the dialog between CD40-CD40 ligand (CD40L). and **CD28** -CD80 counter-receptors on DC and T cells may be linked to HIV infection in vivo.

15/7/38 (Item 34 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08491679 96053185
Blocking CD28/B7 with soluble competitors: immunological phenotype of mCTLA4-H gamma 1 transgenic mice.
Lane P
Basel Institute for Immunology, Switzerland.
Res Immunol (FRANCE) Mar-Apr 1995, 146 (3) p176-9, ISSN 0923-2494
Journal Code: R6E
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
(30 Refs.)

15/7/39 (Item 35 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08474880 96085180
CD28:**B7** interactions promote T cell adhesion.
Turcovski-Corrales SM; Fenton RG; Peltz G; Taub DD
Clinical Services Program, National Cancer Institute-Frederick Cancer Research and Development Center, MD 21702-1201, USA.
Eur J Immunol (GERMANY) Nov 1995, 25 (11) p3087-93, ISSN 0014-2980
Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE

CD28 activation by **antibody**-mediated ligation has been shown to provide an important co-stimulatory signal for T cell adhesion to purified protein ligands. However, the effect of **CD28** ligation by one of its natural ligands, **B7.1**, on T cell adhesion to other cells has not been studied. Therefore, in the present manuscript, we characterized the adhesive interactions between human T cells and **B7.1** -transfected major histocompatibility complex class II+ and class II- melanoma cells. In our studies, human T cells and T cell clones adhered to **B7.1** -transfected melanoma cells, but not to untransfected parental cells. The adhesive reaction in this model was rapid, occurring within 15 min, and was **inhibited** by anti-**B7.1** **antibody** and soluble **CTLA-4** immunoglobulin. **Antibody inhibition** studies demonstrated that adhesion between T cells and **B7.1** -transfected melanoma cells was mediated by interactions between LFA-1:ICAM-1 and CD2:LFA-3. **Inhibition** by pharmacological agents demonstrated that the **CD28**-induced adhesion required specific intracellular signaling events. A protein kinase C

inhibitor, staurosporin, significantly **inhibited** T cell binding to transfected melanoma cells, while cyclosporin A and wortmannin, an **inhibitor** of phosphatidylinositol-3-kinase, did not. These results suggest that the presence of **B7** on various cell populations may activate lymphocytes to adhere better, thus promoting activation, cytolysis, and migration.

15/7/40 (Item 36 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08417189 95363067
Antigen-dependent clonal expansion of a trace population of antigen-specific CD4+ T cells in vivo is dependent on **CD28** costimulation and **inhibited** by **CTLA-4**.
Kearney ER; Walunas TL; Karr RW; Morton PA; Loh DY; Bluestone JA; Jenkins MK
Department of Microbiology, University of Minnesota Medical School, Minneapolis 55455, USA.
J Immunol (UNITED STATES) Aug 1 1995, 155 (3) p1032-6, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI-27998, AI, NIAID; AI-35296, AI, NIAID; AI-29531, AI, NIAID; +
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The importance of **CD28** costimulation to a primary T cell response in vivo was assessed in an adoptive transfer system where a small population of peptide-specific CD4+ TCR transgenic T cells can be physically tracked. Ag-dependent clonal expansion of the transgenic T cells in draining lymph nodes was **blocked** by cyclosporin A and required a **CD28** signal that was completely **inhibited** by **CTLA-4** -Ig or a combination of anti-**B7-1** and anti-**B7**-2 mAbs, but not by either Ab alone. In vivo treatment with the combination of anti-**B7-1** and anti-**B7**-2 mAbs also **blocked** conversion of the Ag-specific T cells to the activated phenotype. In contrast, anti-**CTLA-4** Fab greatly enhanced the in vivo clonal expansion of the Ag-specific T cells. These results suggest that Ag-driven proliferation and phenotype conversion of naive CD4+ T cells is dependent on **CD28** -derived signals and is **inhibited** by **CTLA-4**.

15/7/41 (Item 37 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08417181 95362862
Collagen-induced arthritis in the BB rat. Prevention of disease by treatment with **CTLA-4**-Ig.
Knoerzer DB; Karr RW; Schwartz BD; Mengle-Gaw LJ
Department of Immunology, G.D. Searle and Co., St Louis, Missouri 63198, USA.
J Clin Invest (UNITED STATES) Aug 1995, 96 (2) p987-93, ISSN 0021-9738 Journal Code: HS7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Antigen-specific T cell activation requires two independent signalling events, one mediated through T cell receptor engagement by the antigen-presenting cell-expressed peptide/class II major histocompatibility complex, and the second through the cognate interactions of costimulatory molecules expressed on the T cell and antigen-presenting cell. There is evidence from in vitro and in vivo experimental systems suggesting that the **CD28/B7** costimulatory pathway is crucial for induction of maximal T cell proliferation and T helper-B cell collaboration for IgG production. This pathway can be **blocked** by **CTLA-4**-Ig, a

soluble form of **CTLA-4** which binds with high avidity to the **CD28** ligands, **B7-1** and **B7**-2. Here, we show that **CTLA-4** -Ig treatment prevents clinical and histological manifestations of disease in a collagen-induced arthritis model of rheumatoid arthritis in the diabetes resistant BB/Wor rat, when therapy is initiated before immunization with bovine type II collagen (BIIC). Anti-BIIC **antibody** titers are reduced in **CTLA-4** -Ig-treated rats compared to diseased control animals. Histologically, joints from **CTLA-4** -Ig-treated animals show no histological abnormalities, in contrast to control **antibody**-treated animals, which show complete erosion of the articular cartilage and bone. Despite the efficacy of **CTLA-4**-Ig in preventing clinical and histological signs of arthritis and reducing **antibody** responses to BIIC, delayed type hypersensitivity responses to collagen 18 d or more after **CTLA-4**-Ig treatment ends are similar in **CTLA-4**-Ig-treated and untreated rats, suggesting that the prolonged disease **suppression** observed does not result from induction of T cell anergy.

15/7/42 (Item 38 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08416900 95355845
CD28 and **CTLA-4** have opposing effects on the response of T cells to stimulation [see comments]
Krummel MF; Allison JP
Department of Molecular and Cell Biology, University of California, Berkeley 94720, USA.
J Exp Med (UNITED STATES) Aug 1 1995, 182 (2) p459-65, ISSN 0022-1007 Journal Code: I2V
Contract/Grant No.: CA40041, CA, NCI; CA09179, CA, NCI
Comment in J Exp Med 1995 Aug 1;182(2):289-92
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The importance of the **B7/CD28/CTLA-4** molecules has been established in studies of antigen-presenting cell-derived **B7** and its interaction with the T cell costimulatory molecule **CD28**. **CTLA-4**, a T cell surface glycoprotein that is related to **CD28**, can also interact with **B7-1** and **B7** -2. However, less is known about the function of **CTLA-4**, which is expressed at highest levels after activation. We have generated an **antibody** to **CTLA-4** to investigate the consequences of engagement of this molecule in a carefully defined system using highly purified T cells. We show here that the presence of low levels of **B7** -2 on freshly explanted T cells can partially **inhibit** T cell proliferation, and this **inhibition** is mediated by interactions with **CTLA-4**. Cross-linking of **CTLA-4** together with the TCR and **CD28** strongly **inhibits** proliferation and IL-2 secretion by T cells. Finally, results show that **CD28** and **CTLA-4** deliver opposing signals that appear to be integrated by the T cell in determining the response to activation. These data strongly suggest that the outcome of T cell antigen receptor stimulation is regulated by **CD28** costimulatory signals, as well as **inhibitory** signals derived from **CTLA-4**.

15/7/43 (Item 39 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08416486 95347410
Activation of human peripheral blood dendritic cells induces the CD86 co-stimulatory molecule [published erratum appears in Eur J Immunol 1995 Dec;25(12):3525]

McLellan AD; Starling GC; Williams LA; Hock BD; Hart DN
Haematology/Immunology, Research Laboratory, Christchurch Hospital, New Zealand.
Eur J Immunol (GERMANY) Jul 1995, 25 (7) p2064-8, ISSN 0014-2980 Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Maximal T lymphocyte responses require presentation of antigen by major histocompatibility complex molecules and delivery of one or more co-stimulatory signals. Interaction of the **CD28** molecule on T lymphocytes with its ligands on antigen-presenting cells (APC) initiates a critical co-stimulatory pathway inducing T lymphocyte proliferation and cytokine secretion. Dendritic cells (DC) are potent APC for a primary T lymphocyte response and potential **CD28/CTLA-4** ligands on DC are, therefore, of particular functional relevance. In these experiments, the expression and function of the **CD28/CTLA-4** ligands **B7.1** (CD80) and **B7**.2 (CD86) were examined on human blood DC. Resting DC populations directly isolated by immunodepletion of lineage marker-positive cells lacked cell membrane expression of CD80 and expressed little or no CD86, although CD86, but not CD80 mRNA was detected by reverse transcription-polymerase chain reaction analysis. In contrast, low-density DC isolated after culture in vitro strongly expressed CD86 surface protein, but expressed limited or no CD80, although mRNA for both molecules were detected. Short-term culture of directly isolated DC up-regulated both CD80 and CD86 expression. Analysis of the kinetics of **CD28/CTLA-4** ligand induction showed that surface CD86 was present within 8 h, whereas CD80 antigen was first detected after 24 h of culture. The functional importance of **CD28/CTLA-4** ligand up-regulation on DC during T lymphocyte interactions was demonstrated by the ability of both CTLA-4Ig and CD86 monoclonal **antibodies** (mAb), but not CD80 mAb, to **block** an allogeneic mixed lymphocyte reaction stimulated by DC populations initially negative for CD80 and CD86. These results demonstrate that CD86 is both the earliest and functionally the predominant co-stimulatory **CD28/CTLA-4** ligand on DC.

15/7/44 (Item 40 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08415858 95332711
Cellular interaction in germinal centers. Roles of CD40 ligand and **B7**-2 in established germinal centers.
Han S; Hathcock K; Zheng B; Kepler TB; Hodes R; Kelsoe G
Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore 21201, USA.
J Immunol (UNITED STATES) Jul 15 1995, 155 (2) p556-67, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI-24335, AI, NIAID; AG-10207, AG, NIA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Costimulatory interactions between T and B lymphocytes are crucial for T cell activation and B cell proliferation and differentiation. We have compared the roles of CD40L and **B7**-2 in the initiation and maturation of humoral immunity by administering anti-CD40 ligand (L) or anti-**B7**-2 Ab during the early (days -1 to 3) or late (days 6-10) phases of primary responses to thymus-dependent (Td) and -independent (Ti) Ags. Germinal center (GC) formation in response to a Td Ag was **inhibited** completely by the early administration of anti-CD40L or anti-**B7**-2 Abs. Later in the response, established GCs remained sensitive to anti-CD40L but were resistant to treatment with anti-**B7**-2. However, Ig hypermutation was reduced dramatically in GCs of anti-**B7**-2-treated mice and humoral memory was impaired. Early administration of anti-CD40L reduced serum Ab levels to approximately 10% of controls, whereas early treatment with anti-

B7 -2 reduced Ab production by only 50%. Later treatments with either Ab had no effect on Ab production. Response to a type II Ti Ag was more resistant than Td responses to interruption of costimulatory interactions. Our findings suggest that the costimulatory roles of CD40:CD40L and **B7**-2:**CD28/CTLA-4** differ in the GC; administration of anti-CD40L abrogates an established GC reaction, whereas Ab to **B7** -2 **suppresses** Ig hypermutation and entry into the B cell memory compartment. Once B cells have entered the **differentiation** pathway to Ab production, neither CD40L nor **B7** -2 is necessary for their continued differentiation and persistence.

15/7/45 (Item 41 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08412394 95244885

Coblockade of the LFA1:ICAM and **CD28**/CTLA4:**B7** pathways is a highly effective means of preventing acute lethal graft-versus-host disease induced by fully major histocompatibility complex-disparate donor grafts.

Blazar BR; Taylor PA; Panoskaltsis-Mortari A; Gray GS; Vallera DA
Department of Pediatrics, University of Minnesota Hospital and Clinic, Minneapolis 55455, USA.

Blood (UNITED STATES) May 1 1995, 85 (9) p2607-18, ISSN 0006-4971
Journal Code: A8G
Contract/Grant No.: R01-AI34495, AI, NIAID; ROI-CA 31618, CA, NCI; P01-AI35296, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE

We have developed an in vitro system in which C57BL/6 donor splenocytes are exposed to B10.BR host alloantigens in the context of deficient **CD28**:**B7** signaling as a means of preventing graft-versus-host disease (GVHD). Although 54% to 82% of MLR alloresponse was **inhibited** by cytotoxic T-lymphocyte antigen 4 (CTLA4)-Ig treatment of host stimulator cells, treated splenocytes were still capable of causing GVHD when infused in vivo. By adding anti-leukocyte function antigen 1 (anti-LFA1) **antibody** to hCTLA4-Ig in vitro to coblock the LFA1:intercellular adhesion molecule (ICAM) signaling, splenic alloresponse was **inhibited** by > or = 89%, yet GVHD induction capabilities were retained. Because antigen-primed cells might be more susceptible to **CD28**:**B7** **blockade** , we investigated whether hCTLA4-Ig alone, anti-LFA1 **antibody** alone, or the combination of both added to donor-antihost in vitro primed cells could reduce GVHD. To facilitate hyporesponsiveness induction and to **block B7** and ICAM ligands that are upregulated during GVHD, these reagents were also administered to recipients post-BMT. We have shown that hCTLA4-Ig plus anti-LFA1 **antibody** is highly effective in preventing GVHD-induced lethality (88% to 100% of treated mice surviving versus 0% to 28% of controls surviving). For optimal prevention, both hCTLA4-Ig and anti-LFA1 must be used in vitro in the context of donor-antihost primed splenocytes and continued in vivo. This in vitro-in vivo combined approach was associated with donor engraftment, and recipients were not globally immunosuppressed. We conclude that **blocking** both the **CD28**/**B7** and the LFA1:ICAM pathways are critical to effective GVHD prevention and may offer advantages to in vitro donor T-cell removal.

15/7/46 (Item 42 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08410493 95180287

CD28 functions as an adhesion molecule and is involved in the regulation of human IgE synthesis.

Life P; Aubry JP; Estoppey S; Schnuriger V; Bonnefoy JY

Glaxo Institute for Molecular Biology, Geneva.
Eur J Immunol (GERMANY) Feb 1995, 25 (2) p333-9, ISSN 0014-2980
Journal Code: EN5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Activated T cells induce IgE switching in B cells via a combination of lymphokines and direct T:B cell contact. As **CD28**-deficient mice have reduced basal levels of IgG1 and IgG2a and diminished Ig class switching, we investigated whether the **CD28/B7.1** (CD80) ligand pairing might also be involved in human IgE regulation. Co-incubation of an allergen-specific, human T cell clone with tonsillar B cells caused a marked up-regulation of **CD28** expression, whereas, in contrast, CD45 RB expression was unaffected. To test whether **blocking** the **CD28** : **B7.1** interaction affected IgE synthesis, a dialyzed anti-**CD28** monoclonal **antibody** (mAb) was added to cultures containing tonsillar B cells, pre-activated T cell clones and interleukin-4. Anti-**CD28** treatment caused a reproducible, dose-dependent **inhibition** of IgE, but not IgG synthesis that was accompanied by a visible decrease in cell aggregate formation. Conversely, an anti-**B7.1** mAb had no effect in this system. The effect of **blocking** **CD28**-ligand interactions on lymphocyte adhesion was formally assessed on human T cell clones and B cell lines using dual intracellular staining and flow cytometry. Co-incubation with an anti-**CD28** mAb, but not control IgG or anti-**B7.1** mAb, resulted in a marked impairment of conjugate formation that correlated well with T cell surface expression of **CD28** . Using this system we found that an anti-**CTLA-4** mAb but not an anti-**B7**.2 mAb **inhibited** T:B cell conjugate formation. Lastly, in addition to a direct effect of anti-**CD28** mAb on conjugate formation, 14-day culture of T and B cells in the presence of anti-**CD28** caused a marked decrease of ICAM-1 (CD54) expression on aggregated lymphocytes. In contrast, LFA-1 (CD18) expression was unaffected. We, therefore, conclude that the T cell co-stimulatory molecule **CD28** is involved in the regulation of IgE synthesis in vitro. **CD28** may act to a limited extent as an adhesion molecule, though apparently not by pairing with **B7.1** or **B7**.2. It is more likely that ligation of **CD28** under certain conditions modulates the expression of other T and B cell surface molecules.

15/7/47 (Item 43 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08181061 95053714
B70/**B7** -2 is identical to CD86 and is the major functional ligand for **CD28** expressed on human dendritic cells.
Caux C; Vanbervliet B; Massacrier C; Azuma M; Okumura K; Lanier LL; Banchereau J
Laboratory for Immunological Research, Schering-Plough, Dardilly, France.
J Exp Med (UNITED STATES) Nov 1 1994, 180 (5) p1841-7, ISSN 0022-1007
Journal Code: I2V
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Dendritic cells comprise a system of highly efficient antigen-presenting cells involved in the initiation of T cell responses. Herein, we investigated the role of the **CD28** pathway during alloreactive T cell proliferation induced by dendritic-Langerhans cells (D-Lc) generated by culturing human cord blood CD34+ progenitor cells with granulocyte/macrophage colony-stimulating factor and tumor necrosis factor alpha. In addition to expressing CD80 (**B7**/BB1), a subset of D-Lc expressed B70/**B7** -2. Binding of the CTLA4-Ig fusion protein was completely **inhibited** by a combination of monoclonal **antibodies** (mAbs) against CD80 and B70/**B7** -2, indicating the absence of expression of a third ligand for **CD28/CTLA-4**. It is interesting to note that mAbs against CD86 completely prevented the binding

of CTLA4-Ig in the presence of mAbs against CD80 and bound to a B70/**B7**-2-transfected fibroblast cell line, demonstrating that the B70/**B7**-2 antigen is identical to CD86. **CD28** triggering was essential during D-Lc-induced alloreaction as it was **inhibited** by mAbs against **CD28** (9 out of 11 tested). However, none of six anti-CD80 mAbs demonstrated any activity on the D-Lc-induced alloreaction, though some were previously described as **inhibitory** in assays using CD80-transfected cell lines. In contrast, a mAb against CD86 (IT-2) was found to **suppress** the D-Lc-dependent alloreaction by 70%. This **inhibitory** effect was enhanced to > or = 90% when a combination of anti-CD80 and anti-CD86 mAbs was used. The present results demonstrate that D-Lc express, in addition to CD80, the other ligand for **CTLA-4**, CD86 (B70/**B7** -2), which plays a primordial role during D-Lc-induced alloreaction.

15/7/48 (Item 44 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08173278 94264337

In vivo **blockade** of **CD28**/CTLA4: **B7**/BB1 interaction with CTLA4-Ig reduces lethal murine graft-versus-host disease across the major histocompatibility complex barrier in mice.

Blazar BR; Taylor PA; Linsley PS; Vallera DA

Department of Pediatrics, University of Minnesota Hospital and Clinic, Minneapolis.

Blood (UNITED STATES) Jun 15 1994, 83 (12) p3815-25, ISSN 0006-4971 Journal Code: A8G

Contract/Grant No.: RO1-CA31618, CA, NCI; RO1-CA36725, CA, NCI; PO1-CA21737, CA, NCI; +

Languages: ENGLISH

Document type: JOURNAL ARTICLE

We tested whether the in vivo infusion of recombinant, soluble CTLA4 fused with Ig heavy chains, as a surrogate ligand used to **block** **CD28** /CTLA4 T-cell costimulation, could prevent efficient T-cell activation and thereby reduce graft-versus-host disease (GVHD). Lethally irradiated B10.BR recipients of major histocompatibility complex disparate C57BL/6 donor grafts received intraperitoneal injections of human CTLA4-Ig (hCTLA4-Ig) or murine CTLA4-Ig (mCTLA4-Ig) in various doses and schedules beginning on day -1 or day 0 of bone marrow transplantation (BMT). In all five experiments, recipients of CTLA4-Ig had a significantly higher actuarial survival rate compared to mice injected with an irrelevant **antibody** control (L6) or saline alone. Survival rates in recipients of hL6 or PBS were 0% at 29 to 45 days post-BMT. In recipients of CTLA4-Ig, survival rates were as high as 63% mice surviving 3 months post-BMT. However, protection was somewhat variable and recipients of CTLA4-Ig were not GVHD-free by body weight, clinical appearance, and histopathologic examination. There were no significant differences in the survival rates in comparing injection dose, injection duration, or species of CTLA4-Ig (hCTLA4-Ig v mCTLA4-Ig). Splenic and peripheral blood flow cytometry studies of long-term hCTLA4-Ig-injected survivors showed a significant peripheral B-cell and CD4+ T-cell lymphopenia, consistent with GVHD. A kinetic study of splenic reconstitution was performed in mice that received hCTLA4-Ig and showed that mature splenic localized CD8+ T-cell repopulation was not significantly different in recipients of hCTLA4-Ig compared with hL6, despite the significant increase in actuarial survival rate in that experiment. These data suggest that the beneficial effect of hCTLA4-Ig on survival is not mediated by interfering with mature donor-derived T-cell repopulation post-BMT. Neither hCTLA4-Ig nor mCTLA4-Ig interfered with hematopoietic recovery post-BMT. We conclude that CTLA4-Ig (most likely in combination with other agents) may represent an important new modality for GVHD prevention.

15/7/49 (Item 45 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08167998 94100531
Synergy between cyclosporin A and a monoclonal **antibody** to **B7** in **blocking** alloantigen-induced T-cell activation.
Van Gool SW; Ceuppens JL; Walter H; de Boer M
Department of Pathophysiology, Catholic University of Leuven, Belgium.
Blood (UNITED STATES) Jan 1 1994, 83 (1) p176-83, ISSN 0006-4971
Journal Code: A8G
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Costimulatory signals are absolutely required for T-cell activation after T-cell receptor/major histocompatibility complex-peptide interaction. So far, the best-known candidate essential costimulatory signal is mediated by interaction of **CD28** on T cells with **B7** on antigen-presenting cells. Using an allogeneic **B7**+ Epstein-Barr virus-transformed B-cell line as stimulator, we found that addition of a monoclonal **antibody** (MoAb) to **B7** that efficiently **blocks** **B7-CD28** interaction only partially **inhibited** proliferation and interleukin-2 (IL-2) production in primary and secondary mixed lymphocyte reactions (MLR), whereas the generation of cytotoxic T lymphocytes (CTL) was not affected. **Inhibition** of primary or secondary MLR-induced T-cell activation with cyclosporin A (CsA) at nontoxic concentrations also was never complete. However, the combination of CsA and anti-**B7** MoAb **B7**-24 synergistically **blocked** allogeneic B cell-induced T-cell proliferation, IL-2 production, and CTL generation. These data suggest that the mere **blockage** of **B7-CD28** interaction during allotransplantation will be insufficient to prevent rejection or graft-versus-host disease. However, low CsA concentrations, when combined with an agent **blocking** **B7-CD28** interaction, can potentially achieve complete immunosuppression.

15/7/50 (Item 46 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07803298 94068568
Evidence for an additional ligand, distinct from **B7**, for the **CTLA-4** receptor.
Razi-Wolf Z; Galvin F; Gray G; Reiser H
Division of Lymphocyte Biology, Dana-Farber Cancer Institute, Boston, MA 02115.
Proc Natl Acad Sci U S A (UNITED STATES) Dec 1 1993, 90 (23) p11182-6, ISSN 0027-8424 Journal Code: PV3
Contract/Grant No.: AI-33679, AI, NIAID
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Activation of T lymphocytes requires the recognition of peptide-major histocompatibility complex complexes and costimulatory signals provided by antigen-presenting cells (APCs). The best-characterized costimulatory molecule to date is the **B7** antigen, a member of the immunoglobulin family that binds two receptors, **CD28** and **CTLA-4** , expressed on the T-cell surface. Using the anti-mouse **B7** (mB7) monoclonal **antibody** (mAb) 16-10A1, which we recently developed, we found that mB7 is indeed an important costimulatory ligand for the antigen-specific activation of murine T cells by B lymphocytes. Three lines of evidence suggest, however, the existence of at least one additional ligand for the **CTLA-4** receptor. First, a soluble fusion protein of human **CTLA-4** and the IgG1 Fc region, termed CTLA4Ig, **blocks** better than the anti-mB7 mAb the allogeneic stimulation of T cells by unfractionated splenic APCs. Second, saturating amounts of anti-mB7 mAb do not significantly **block** binding of fluorescein

isothiocyanate-conjugated CTLA4Ig to activated splenic APCs. Furthermore, CTLA4Ig but not the anti-mB7 mAb reacts with the M12 and M12.C3 cell lines. The identification of an additional ligand for **CTLA-4** may have applications to the treatment of autoimmune disease and transplant-associated disorders.

15/7/51 (Item 47 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07802381 94050123
B70 antigen is a second ligand for **CTLA-4** and **CD28**.
Azuma M; Ito D; Yagita H; Okumura K; Phillips JH; Lanier LL; Somoza C
Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan.
Nature (ENGLAND) Nov 4 1993, 366 (6450) p76-9, ISSN 0028-0836 Journal Code: NSC
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The membrane antigen **B7**/BB1 (refs 1, 2) is expressed on activated B cells, macrophages and dendritic cells, and binds to a counter-receptor, **CD28**, expressed on T lymphocytes and thymocytes. Interaction between **CD28** and **B7** results in potent costimulation of T-cell activation initiated through the CD3/T-cell receptor complex. Discrepancies between results with anti-**CD28** and anti-**B7 antibodies** have suggested the existence of a second ligand for **CD28** and **CTLA-4** (refs 3, 6-8). We have generated a monoclonal **antibody**, IT2, that reacts with a 70K glycoprotein (B70). B70 complementary DNA was cloned from a B-lymphoblastoid cell line library and encodes a new protein of the immunoglobulin superfamily with limited homology to **B7**. B70 is expressed on resting monocytes and dendritic cells and on activated, but not resting, T, NK and B lymphocytes. IT2 substantially **inhibited** the binding of a CTLA4-immunoglobulin fusion protein to human B-lymphoblastoid cell lines and, together with anti-**B7 antibody**, completely **blocked CTLA-4** binding. Further IT2 efficiently **inhibited** primary allogeneic mixed lymphocyte responses. These findings indicate that B70 is a second ligand for **CD28** and **CTLA-4** and may play an important role for costimulation of T cells in a primary immune response.

15/7/52 (Item 48 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07792567 93224730
CD28 ligation by monoclonal **antibodies** or **B7**/BB1 provides an accessory signal for the cyclosporin A-resistant generation of cytotoxic T cell activity.
Van Gool SW; de Boer M; Ceuppens JL
Department of Pathophysiology, Catholic University of Leuven, Belgium.
J Immunol (UNITED STATES) Apr 15 1993, 150 (8 Pt 1) p3254-63, ISSN 0022-1767 Journal Code: IFB
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Ligation of the T cell membrane Ag **CD28** with mAb 9.3 or with its natural ligand **B7**/BB1 on accessory cells has been shown to provide a helper signal for stimulation through the TCR/CD3 complex. The present study was undertaken to investigate whether **CD28** could function as an accessory signal receptor in the generation and effector phase of CTL activity. Purified resting human T cells were activated for 3 to 4 days with immobilized anti-CD3 mAb as the primary stimulus, and CTL activity was then measured by an anti-CD3-redirected 4-hr 51Cr release assay on Fc gamma R-bearing P815 target cells. When the concentration of immobilized anti-CD3

mAb as the primary signal for CTL generation was below threshold, CTL activity could be generated by addition of mAb 9.3 to the cultures. At optimal concentrations of immobilized anti-CD3, the addition of anti-**CD28** did not further enhance the generation of CTL activity, but under these conditions generation of CTL activity was almost completely resistant to cyclosporin A (CsA) as a result of CsA-resistant IL-2 production. When 3T6 mouse fibroblasts, transfected with Fc gamma RII and **B7**, were used as accessory cells, anti-CD3 and **B7** were also found to generate cytotoxic activity. Cytotoxic T cell generation under these conditions could be **blocked** by anti-**B7** mAb, but was totally resistant to CsA. CTL activity could be generated by CD3 and **CD28** ligation in both CD4(+) and CD8(+) subpopulations. Finally, we found that the activity of CTL lines (isolated from ascitic fluid of a patient with ovarian carcinoma and cultured in IL-2) was higher on **B7** -transfected targets than on the **B7**(-) targets. We conclude that **CD28** ligation provides a major accessory signal for the CsA-resistant generation of CTL activity and that **CD28-B7** interaction also enhances cytotoxic effector functions of CTL. These findings might have important implications for immunotherapeutic interventions.

15/7/53 (Item 49 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

07302322 93094763

Coexpression and functional cooperation of **CTLA-4** and **CD28** on activated T lymphocytes.

Linsley PS; Greene JL; Tan P; Bradshaw J; Ledbetter JA; Anasetti C; Damle NK

Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, Washington 98121.

J Exp Med (UNITED STATES) Dec 1 1992, 176 (6) p1595-604, ISSN 0022-1007 Journal Code: I2V

Languages: ENGLISH

Document type: JOURNAL ARTICLE

T cell costimulation by molecules on the antigen presenting cell (APC) is required for optimal T cell proliferation. The **B7** molecule on APC binds the T lymphocyte receptor **CD28** , triggering increased interleukin 2 (IL-2) production and subsequent T cell proliferation. **CTLA-4** is a predicted T cell membrane receptor homologous to **CD28**, which also binds the **B7** counter receptor, but whose distribution and function are unknown. Here we have developed monoclonal **antibodies** (mAbs) specific for **CTLA-4** and have investigated these questions. mAbs were produced that bound **CTLA-4** but not **CD28**, and that **blocked** binding of **CTLA-4** to **B7**. **CTLA-4** expression as measured by these mAbs was virtually undetectable on resting T cells, but was increased several hundred-fold during T cell activation. On activated lymphocytes, **CTLA-4** was expressed equally on CD4+ and CD8+ T cell subsets and was coexpressed with CD25, **CD28**, and CD45RO. **CTLA-4** expression was lower than that of **CD28** , reaching a maximum of approximately 1/30-50 the level of **CD28** . Despite its lower expression, **CTLA-4** was responsible for much of the **B7** binding by large activated T cells. Anti-**CTLA-4** mAb 11D4 and anti-**CD28** mAb 9.3 acted cooperatively to **inhibit** T cell adhesion to **B7**, and to **block** T cell proliferation in primary mixed lymphocyte culture. When coimmobilized with anti T cell receptor (TCR) mAb, anti-**CTLA-4** mAbs were less effective than anti-**CD28** mAb 9.3 at costimulating proliferation of resting or activated T cells. However, coimmobilized combinations of anti-**CD28** and anti-**CTLA-4** were synergistic in their ability to augment anti-TCR-induced proliferation of preactivated CD4+ T cells. These results indicate that **CTLA-4** is coexpressed with **CD28** on activated T lymphocytes and cooperatively regulates T cell adhesion and

activation by **B7**.

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     $0.13  Estimated cost this search
     $0.13  Estimated total session cost   0.041 DialUnits

File 410:Chronolog(R)  1981-1998/Jul/Aug
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     $0.00  Estimated cost this search
     $0.13  Estimated total session cost   0.148 DialUnits

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  File  72:EMBASE  1985-1998/Aug W2
        (c) 1998 Elsevier Science B.V.
  File 154:MEDLINE(R)  1985-1998/Sep W4
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Ref   Items  Index-term
E1        1  AU=ANDERSON, DARREL R.
E2        2  AU=ANDERSON, DARRELL
E3        0 *AU=ANDERSON, DARRELL ?
E4        1  AU=ANDERSON, DARRELL E.
E5       15  AU=ANDERSON, DARRELL R.
E6        1  AU=ANDERSON, DARRELL RAY
E7        5  AU=ANDERSON, DARWIN W.
E8        1  AU=ANDERSON, DARWIN WAYNE
E9        1  AU=ANDERSON, DARYL J.
E10       1  AU=ANDERSON, DARYL M.
E11       2  AU=ANDERSON, DAVE
E12       1  AU=ANDERSON, DAVE A.

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             15  AU=ANDERSON, DARRELL R.
              1  AU=ANDERSON, DARRELL RAY
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? rd s1

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
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 2/7/1     (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)
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  129027008    CA: 129(3)27008c    PATENT
  Identification of unique binding interactions between certain antibodies
and the human b7.1 and b7.2 co-stimulatory antigens
  INVENTOR(AUTHOR): Anderson, Darrell R.; Hanna, Nabil; Brams, Peter
  LOCATION: USA
  ASSIGNEE: Idec Pharmaceuticals Corporation
  PATENT: PCT International ; WO 9819706 A1  DATE: 19980514
  APPLICATION: WO 97US19906 (19971029) *US 746361 (19961108)
  PAGES: 87 pp.  CODEN: PIXXD2  LANGUAGE: English  CLASS: A61K-039/395A;
C07K-016/18B; C07K-016/28B  DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BA;
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BB; BG; BR; BY; CA; CH; CN; CU; CZ; DE; DK; EE; ES; FI; GB; GE; GH; HU; ID; IL; IS; JP; KE; KG; KP; KR; KZ; LC; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG; SI; SK; SL; TJ; TM; TR; TT; UA; UG; UZ; VN; YU; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM
DESIGNATED REGIONAL: GH; KE; LS; MW; SD; SZ; UG; ZW; AT; BE; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
SECTION:
CA215003 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: monoclonal antibody antigen B7 CD80 CD87, immunosuppressant antibody antigen B7 autoimmune disease
DESCRIPTORS:
Mouse... Primate...
chimeric antibody; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
Allergies... Aplastic anemia... Autoimmune diseases... B cell lymphoma... B cell(lymphocyte)... cDNA sequences... CD28(antigen)... CD80(antigen)... CD86(antigen)... CTLA-4(antigen)... Graft vs. host reaction... Idiopathic thrombocytopenic purpura... Immunosuppressants... Infection... Inflammation ... Insulin dependent diabetes mellitus... Interleukin 2... Monoclonal antibodies... Multiple sclerosis... Protein sequences... Psoriasis... Rheumatoid arthritis... Systemic lupus erythematosus... T cell(lymphocyte) ...
humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
Biliary tract diseases...
inflammatory; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
CAS REGISTRY NUMBERS:
186271-56-7 186271-58-9 186271-60-3 186271-62-5 186271-64-7
208065-43-4 amino acid sequence; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases
186271-55-6 186271-57-8 186271-59-0 186271-61-4 186271-63-6
186271-65-8 nucleotide sequence; humanized or primatized monoclonal antibodies or light and heavy chains for inhibiting antigen B7.1 or B7.2 and for use as immunosuppressant for treating autoimmune diseases

2/7/2 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

128293972 CA: 128(24)293972e PATENT
Therapeutic application of chimeric and radiolabeled antibodies to human B lymphocyte-restricted differentiation antigen for treatment of B cell lymphoma
INVENTOR(AUTHOR): Anderson, Darrell R.; Hanna, Nabil; Leonard, John E.; Newman, Roland A.; Reff, Mitchell E.; Rastetter, William H.
LOCATION: USA
ASSIGNEE: Idec Pharmaceuticals Corporation
PATENT: United States ; US 5736137 A DATE: 19980407
APPLICATION: US 149099 (19931103) *US 978891 (19921113)
PAGES: 50 pp. Cont.-in-part of U.S. Ser. No. 978,891, abandoned. CODEN: USXXAM LANGUAGE: English CLASS: 424133100; A61K-039/395A; C07K-016/30B; C12N-001/21B; C12N-005/20B
SECTION:
CA215003 Immunochemistry
CA203XXX Biochemical Genetics
IDENTIFIERS: B lymphocyte restricted differentiation antigen antibody, lymphoma B cell CD20 chimeric antibody

DESCRIPTORS:
Antigens...
B lymphocyte-restricted differentiation; chimeric anti-CD20 antibodies for treatment of B cell lymphomas
Antibodies... B cell lymphoma... Buffers... CD20(antigen)... DNA sequences ... Drug carriers(drug delivery systems)... Physiological saline solutions ... Protein sequences...
chimeric anti-CD20 antibodies for treatment of B cell lymphomas
CAS REGISTRY NUMBERS:
157754-00-2 205945-40-0 amino acid sequence; chimeric anti-CD20 antibodies for treatment of B cell lymphomas
57-55-6 biological studies, chimeric anti-CD20 antibodies for treatment of B cell lymphomas
157754-01-3 205945-39-7 205945-41-1 nucleotide sequence; chimeric anti-CD20 antibodies for treatment of B cell lymphomas

2/7/3 (Item 3 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

126117055 CA: 126(9)117055h PATENT
Macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
INVENTOR(AUTHOR): Anderson, Darrell R.; Brams, Peter; Hanna, Nabil; Shestowsky, William S.
LOCATION: USA
ASSIGNEE: Idec Pharmaceuticals Corporation
PATENT: PCT International ; WO 9640878 A1 DATE: 19961219
APPLICATION: WO 96US10053 (19960606) *US 487550 (19950607)
PAGES: 80 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: C12N-005/12A; A61K-039/395B; C07K-016/00B DESIGNATED COUNTRIES: AL; AM; AT; AU; AZ; BB; BG; BR; BY; CA; CH; CN; CZ; DE; DK; EE; ES; FI; GB; GE; HU; IL; IS; JP; KE; KG; KP; KR; KZ; LK; LR; LS; LT; LU; LV; MD; MG; MK; MN; MW; MX; NO; NZ; PL; PT; RO; RU; SD; SE; SG DESIGNATED REGIONAL: KE; LS; MW; SD; SZ; UG; AT; BE ; CH; DE; DK; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN
SECTION:
CA215003 Immunochemistry
IDENTIFIERS: B7 antigen monoclonal antibody macaque
DESCRIPTORS:
Interleukin 2...
anti-B7 antibodies inhibit synthesis of; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
Immunosuppressants...
antibodies to B7 antigens as; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
T-cell activation...
antibodies to B7 antigens for inhibition of; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
cDNA sequences...
for anti-B7 antibodies of macaque; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
Genes(animal)...
for macaque Igs; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
CD80(antigen)... Macaca... Monoclonal antibodies...
macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
Protein sequences...

of anti-B7 antibodies of macaque; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
CAS REGISTRY NUMBERS:
186271-56-7 186271-58-9 186271-60-3 186271-62-5 186271-64-7
186271-66-9 amino acid sequence; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants
186271-55-6 186271-57-8 186271-59-0 186271-61-4 186271-63-6
186271-65-8 nucleotide sequence; macaque monoclonal antibodies specific to human B7.1 or B7.2 antigens and primatized forms and their use as immunosuppressants

2/7/4 (Item 4 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

121170532 CA: 121(15)170532j PATENT
Chimeric and radiolabeled antibodies to human B lymphocyte restricted differentiation antigens for treatment of B cell lymphoma
INVENTOR(AUTHOR): Anderson, Darrell R.; Rastetter, William H.; Hanna, Nabil; Leonard, John E.; Newman, Roland A.; Reff, Mitchell E.
LOCATION: USA
ASSIGNEE: Idec Pharmaceuticals Corp.
PATENT: PCT International ; WO 9411026 A2 DATE: 940526
APPLICATION: WO 93US10953 (931112) *US 978891 (921113)
PAGES: 101 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A61K-039/395A; A61K-043/00B; C12N-015/02B; C12P-021/08B DESIGNATED COUNTRIES: AT; AU; BB; BG; BR; BY; CA; CH; CZ; DE; DK; ES; FI; GB; HU; JP; KP; KR; KZ; LK; LU; MG; MN; MW; NL; NO; NZ; PL; PT; RO; RU; SD; SE; SK; UA; UZ; VN
DESIGNATED REGIONAL: AT; BE; CH; DE; DK; ES; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE; BF; BJ; CF; CG; CI; CM; GA; GN; ML; MR; NE; SN; TD; TG
SECTION:
CA201006 Pharmacology
CA215XXX Immunochemistry
IDENTIFIERS: CD20 antibody chimeric B lymphoma
DESCRIPTORS:
Antigens,CD20...
chimeric antibodies to, for treatment of B lymphoma
Antibodies... Antibodies,monoclonal, indium complexes, labeled with indium-111... Antibodies,monoclonal, yttrium complexes, labeled with yttrium-90...
chimeric, humanized, to CD20 antigens, for treatment of B-lymphoma
Gene,chimeric...
for humanized antibodies to CD20 antigens, expression in CHO and SP2/0 cells of
Deoxyribonucleic acid sequences...
of mouse and chimeric genes for humanized antibodies to CD20 antigens
Protein sequences...
of variable regions of monoclonal antibody to CD20 antigens, of mouse
Plasmid and Episome...
TCAE 8, chimeric genes for humanized antibodies to CD20 antigens on, in prepn. antibodies for treatment of B-lymphoma
Lymphoma,B-cell...
treatment of, humanized mouse antibodies CD20 antigen for
CAS REGISTRY NUMBERS:
157754-00-2 157754-02-4 amino acid sequence of, prepn. humanized anti-CD20 antibodies for treatment of B-lymphoma in relation to
157753-96-3 157753-97-4 157753-98-5 nucleotide sequence of
157753-99-6 157754-01-3 nucleotide sequence of, in prepn. humanized anti-CD20 antibodies, treatment of B-lymphoma in relation to

2/7/5 (Item 5 from file: 399)

DIALOG(R)File 399:CA SEARCH(R)

120104493 CA: 120(9)104493a JOURNAL
Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20
AUTHOR(S): Reff, Mitchell E.; Carner, Kristin; Chambers, Karen S.; Chinn, Paul C.; Leonard, John E.; Raab, Ron; Newman, Roland A.; Hanna, Nabil; Anderson, Darrell R.
LOCATION: IDEC Pharm. Corp., San Diego, CA, 92121, USA
JOURNAL: Blood DATE: 1994 VOLUME: 83 NUMBER: 2 PAGES: 435-45 CODEN: BLOOAW ISSN: 0006-4971 LANGUAGE: English
SECTION:
CA215003 Immunochemistry
CA201XXX Pharmacology
IDENTIFIERS: monoclonal antibody CD20 B cell depletion, complement dependent lysis antibody CD20, lymphoma B cell anticancer antibody CD20
DESCRIPTORS:
Cytolysis...
complement-dependent, of B cell, chimeric mouse-human monoclonal antibody to CD20 in
Lymphocyte,B-cell...
depletion of, by chimeric mouse-human monoclonal antibodies to CD20 antigen
Neoplasm inhibitors,B-cell lymphoma...
monoclonal antibodies to CD20 antigen as, chimeric mouse-human, B cell depletion in
Antigens,CD20...
monoclonal antibodies to, chimeric mouse-human, B cell depletion by, antitumor in relation to
Antibodies,monoclonal...
to CD20 antigen, chimeric mouse-human, B cell depletion by, antitumor in relation to
CAS REGISTRY NUMBERS:
80295-33-6 binding of, by chimeric mouse-human monoclonal antibody to CD20, in B cell depletion

2/7/6 (Item 6 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

111037819 CA: 111(5)37819k PATENT
Method for selection of antiidiotype antibodies containing the internal image of a pathogen antigen
INVENTOR(AUTHOR): Anderson, Darrel R.
LOCATION: USA
ASSIGNEE: Synbiotics Corp.
PATENT: European Pat. Appl. ; EP 286405 A2 DATE: 881012
APPLICATION: EP 88303109 (880407) *US 36027 (870408)
PAGES: 7 pp. CODEN: EPXXDW LANGUAGE: English CLASS: C07K-003/18A; C12N-005/00B; C12P-021/00B; C12Q-001/24B; A61K-039/395; A61K-039/00; G01N-033/569 DESIGNATED COUNTRIES: AT; BE; CH; DE; ES; FR; GB; GR; IT; LI; LU; NL; SE
SECTION:
CA215003 Immunochemistry
IDENTIFIERS: antiidiotypic antibody antiserum selection, Dirofilaria antiidiotype antibody selection
DESCRIPTORS:
Antiserums...
affinity-purified, in selection of cells producing antibodies to antibodies of pathogens
Microorganism,pathogenic...
antibodies of, antibodies to, cells producing, selection of, affinity-purified antiserum in

Dirofilaria immitis...
antibodies of, antibodies to, hybridomas producing, selection of, affinity-purified antiserum in
Chromatography,column and liquid, preparative, immunoadsorption...
of pathogenic-specific antiserum, antiidiotype antibody selection in relation to
Cell... Hybridoma...
producing antibodies to antibodies of pathogens, selection of, affinity-purified antiserum in
Antibodies...
to antibodies of pathogens, cells producing, selection of, affinity-purified antiserum in

2/7/7 (Item 7 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

105002438 CA: 105(1)2438j JOURNAL
Studies on the carbohydrate moiety of vitellogenin from the tobacco hornworm, Manduca sexta
AUTHOR(S): Osir, Ellie O.; Anderson, Darrell R.; Grimes, William J.; Law, John H.
LOCATION: Dep. Biochem., Biol. Sci., Univ. Arizona, Tucson, AZ, 85721, USA
JOURNAL: Insect Biochem. DATE: 1986 VOLUME: 16 NUMBER: 3 PAGES: 471-8
CODEN: ISBCAN ISSN: 0020-1790 LANGUAGE: English
SECTION:
CA106004 General Biochemistry
CA112XXX Nonmammalian Biochemistry
IDENTIFIERS: tobacco hornworm vitellogenin carbohydrate, vitellogenin carbohydrate Manduca
DESCRIPTORS:
Vitellogenins...
carbohydrates of, of Manduca sexta, structure of
Carbohydrates and Sugars,biological studies...
of vitellogenin, of Manduca sexta, glycosylation process in relation to
Oligosaccharides,mannose-contg....
structure of, of vitellogenin of Manduca sexta
Ovary,follicle,metabolism...
vitellogenin deglycosylated deriv. uptake by, of Manduca sexta
Manduca sexta...
vitellogenin of, carbohydrate structure of
CAS REGISTRY NUMBERS:
78836-79-0 of vitellogenin, of manduca sexta

2/7/8 (Item 8 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

104049617 CA: 104(7)49617m JOURNAL
Major carbohydrate structures at five glycosylation sites on murine IgM determined by high resolution proton NMR spectroscopy
AUTHOR(S): Anderson, Darrell R.; Atkinson, Paul H.; Grimes, William J.
LOCATION: Dep. Biochem., Univ. Arizona, Tucson, AZ, 85721, USA
JOURNAL: Arch. Biochem. Biophys. DATE: 1985 VOLUME: 243 NUMBER: 2
PAGES: 605-18 CODEN: ABBIA4 ISSN: 0003-9861 LANGUAGE: English
SECTION:
CA115003 Immunochemistry
IDENTIFIERS: IgM glycosylation site carbohydrate
DESCRIPTORS:
Immunoglobulins,M...
glycosylation sites of, carbohydrate structures at
Oligosaccharides...

of IgM
Carbohydrates and Sugars,biological studies...
of IgM glycosidation sites
Glycosidation...
sites for, on IgM, carbohydrate structures at
CAS REGISTRY NUMBERS:
67739-90-6 99794-83-9 99794-84-0 99802-34-3 of IgM

2/7/9 (Item 9 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

103209205 CA: 103(25)209205k JOURNAL
Arylphorin from Manduca sexta: carbohydrate structure and immunological studies
AUTHOR(S): Ryan, Robert O.; Anderson, Darrell R.; Grimes, William J.; Law, John H.
LOCATION: Dep. Biochem., Univ. Arizona, Tucson, AZ, 85721, USA
JOURNAL: Arch. Biochem. Biophys. DATE: 1985 VOLUME: 243 NUMBER: 1
PAGES: 115-24 CODEN: ABBIA4 ISSN: 0003-9861 LANGUAGE: English
SECTION:
CA106003 General Biochemistry
IDENTIFIERS: Manduca arylphorin carbohydrate subunit structure
DESCRIPTORS:
Manduca sexta...
arylphorin of, carbohydrate and subunit structure of
Silkworm...
arylphorin of, Manduca sexta arylphorin related to
Hemolymph...
arylphorin of, of Manduca sexta, structure of
Proteins,arylphorins...
carbohydrate and subunit structure of, of Manduca sexta
Carbohydrates and Sugars,biological studies... Molecular structure,natural product, quaternary...
of arylphorin, of Manduca sexta
CAS REGISTRY NUMBERS:
78836-79-0 of arylphorin of Manduca sexta

2/7/10 (Item 10 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

103019362 CA: 103(3)19362m JOURNAL
Application of microcomputers to the interpretation of high-resolution nuclear magnetic resonance spectra of asparagine-linked oligosaccharides: evaluation of high-mannose structures
AUTHOR(S): Anderson, Darrell R.; Grimes, William J.
LOCATION: Dep. Biochem., Univ. Arizona, Tucson, AZ, 85721, USA
JOURNAL: Anal. Biochem. DATE: 1985 VOLUME: 146 NUMBER: 1 PAGES: 13-22
CODEN: ANBCA2 ISSN: 0003-2697 LANGUAGE: English
SECTION:
CA109010 Biochemical Methods
IDENTIFIERS: asparagine linked mannose oligosaccharide NMR, oligosaccharide structure detn NMR computer
DESCRIPTORS:
Oligosaccharides,mannose-contg....
asparagine-linked, structure of, detn. of, by NMR and computer
Molecular structure,natural product...
detn. of, of high-mannose asparagine-linked oligosaccharides by NMR with computer
Computer program...
for NMR structural anal. of high-mannose asparagine-linked oligosaccharides

Glycopeptides... Glycoproteins...
NMR spectra of, computer program for interpretation of
Nuclear magnetic resonance,high-resoln....
of high-mannose asparagine-linked oligosaccharides
CAS REGISTRY NUMBERS:
74424-57-0 structure of, detn. of, by NMR and computer

2/7/11 (Item 11 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

100004528 CA: 100(1)4528j JOURNAL
Incomplete glycosylation of Asn 563 in mouse immunoglobulin M
AUTHOR(S): Anderson, Darrell R.; Samaraweera, Preminda; Grimes, William J.
LOCATION: Dep. Biochem., Univ. Arizona, Tucson, AZ, 85721, USA
JOURNAL: Biochem. Biophys. Res. Commun. DATE: 1983 VOLUME: 116
NUMBER: 2 PAGES: 771-6 CODEN: BBRCA9 ISSN: 0006-291X LANGUAGE: English
SECTION:
CA115003 Immunochemistry
IDENTIFIERS: IgM asparagine residue glycosylation mouse
DESCRIPTORS:
Immunoglobulins,M...
asparagine residue of, incomplete glycosylation of, of mouse
Mouse...
IgM of, asparagine residue of, incomplete glycosylation of
Glycosidation...
of IgM asparagine residue, of mouse
Amino acids,biological studies... Carbohydrates and Sugars,biological studies...
of IgM, of mouse, glycosylation of asparagine residue in relation to

2/7/12 (Item 12 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

98003387 CA: 98(1)3387r JOURNAL
Heterogeneity of asparagine-linked oligosaccharides of five glycosylation sites on immunoglobulin M heavy chain from mineral oil plasmacytoma 104E
AUTHOR(S): Anderson, Darrell R.; Grimes, William J.
LOCATION: Dep. Biochem., Univ. Arizona, Tucson, AZ, 85721, USA
JOURNAL: J. Biol. Chem. DATE: 1982 VOLUME: 257 NUMBER: 24 PAGES: 14858-64 CODEN: JBCHA3 ISSN: 0021-9258 LANGUAGE: English
SECTION:
CA115003 Immunochemistry
IDENTIFIERS: IgM asparagine linkage oligosaccharide, glycosylation IgM heavy chain
DESCRIPTORS:
Immunoglobulins,M...
MORC 104E, heavy chain of, asparagine-linked oligosaccharides of
glycosylation sites of, heterogeneity of
Oligosaccharides,asparagine-linked...
of glycosylation sites, of IgM MOPC 104E heavy chain, heterogeneity of
Protein sequences...
of IgM MOPC 104E heavy chain, asparagine-linked glycosylations sites in relation to
Glycosidation...
sites for, of asparagine-linked oligosaccharides of IgM MOPC 104E heavy chain, heterogeneity of
CAS REGISTRY NUMBERS:
70-47-3 biological studies, -linked oligosaccharides, of glycosidation
sites, of IgM heavy chain of MOPC 104E, heterogeneity of

2/7/13 (Item 13 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

96049901 CA: 96(7)49901r CONFERENCE PROCEEDING
Complex polysaccharides of normal and transformed cells
AUTHOR(S): Grimes, William J.; Anderson, Darrell R.; Van Nest, Gary A.; Lindsey, Julia P.; Bestwick, Linda C.
LOCATION: Coll. Med., Univ. Arizona, Tucson, AZ, 85724, USA
JOURNAL: Growth Requir. Vertebr. Cells in Vitro EDITOR: Waymouth, Charity (Ed), Ham, Richard G. (Ed), Chapple, Paul J (Ed), DATE: 1981
PAGES: 388-400 CODEN: 46YBAF LANGUAGE: English PUBLISHER: Cambridge Univ. Press,Cambridge, Engl
SECTION:
CA114001 Mammalian Pathological Biochemistry
CA113XXX Mammalian Biochemistry
IDENTIFIERS: transformed cell glycoprotein glycolipid
DESCRIPTORS:
Animal cell...
glycolipids and glycoproteins of transformed
Transformation,neoplastic...
glycolipids and glycoproteins of transformed cell in
Glycolipids... Glycoproteins...
of transformed cell

2/7/14 (Item 14 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

88165789 CA: 88(23)165789u DISSERTATION
Calcium effects on human erythrocyte membranes
AUTHOR(S): Anderson, Darrell Ray
LOCATION: Oklahoma State Univ., Stillwater, Okla.
DATE: 1976 PAGES: 104 pp. CODEN: DABBBA LANGUAGE: English CITATION: Diss. Abstr. Int. B 1978, 38(9), 4192 AVAIL: Univ. Microfilms Int., Order No. 7801201
SECTION:
CA006013 General Biochemistry
IDENTIFIERS: calcium erythrocyte membrane, spectrin calcium
DESCRIPTORS:
Spectrins...
calcium effect on
Erythrocyte...
calcium effect on cell membrane of, spectrin in relation to
Cell membrane...
calcium effect on, of erythrocyte, spectrin in relation to
CAS REGISTRY NUMBERS:
7440-70-2 biological studies, erythrocyte membrane response to, spectrin in relation to

2/7/15 (Item 15 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

87147994 CA: 87(19)147994g JOURNAL
Calcium-promoted changes of the human erythrocyte membrane. Involvement of spectrin, transglutaminase, and a membrane-bound protease
AUTHOR(S): Anderson, Darrell R.; Davis, J. Lawrence; Carraway, Kermit L.
LOCATION: Dep. Biochem., Oklahoma State Univ., Stillwater, Okla.
JOURNAL: J. Biol. Chem. DATE: 1977 VOLUME: 252 NUMBER: 19 PAGES: 6617-23 CODEN: JBCHA3 LANGUAGE: English

SECTION:
CA007013 Enzymes
CA013XXX Mammalian Biochemistry
IDENTIFIERS: erythrocyte membrane polypeptide calcium, transglutaminase crosslinking erythrocyte membrane calcium, spectrin crosslinking erythrocyte membrane calcium, proteinase erythrocyte membrane polypeptide calcium
DESCRIPTORS:
Erythrocyte...
calcium-induced membrane changes in, transglutaminase and protease in relation to
Spectrins...
of erythrocyte membrane, calcium-induced crosslinking of, transglutaminase in relation to
CAS REGISTRY NUMBERS:
7440-70-2 biological studies, erythrocyte membrane changes in response to, transglutaminase and protease in relation to
9031-65-6 calcium-induced erythrocyte membrane polypeptide crosslinking by
9001-92-7 of erythrocyte membrane, calcium-induced activation of

2/7/16 (Item 16 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

85155404 CA: 85(21)155404p JOURNAL
Cytoskeletal proteins associated with cell surface envelopes from sarcoma 180 ascites tumor cells
AUTHOR(S): Moore, Pamela B.; Anderson, Darrell R.; Huggins, John W.; Carraway, Kermit L.
LOCATION: Dep. Biochem., Oklahoma State Univ., Stillwater, Okla.
JOURNAL: Biochem. Biophys. Res. Commun. DATE: 1976 VOLUME: 72 NUMBER: 1 PAGES: 288-94 CODEN: BBRCA9 LANGUAGE: English
SECTION:
CA906013 General Biochemistry
CA913XXX Mammalian Biochemistry
CA914XXX Mammalian Pathological Biochemistry
IDENTIFIERS: muscle protein sarcoma membrane
DESCRIPTORS:
Spectrins...
-like proteins, of cell membrane of sarcoma, cell shape and motility in relation to
Proteins...
muscle-like, of membrane of sarcoma, cell shape and mobility in relation to
Animal cell... Cell membrane...
muscle-like proteins of, cell shape and motility in relation to
Sarcoma...
muscle-like proteins of membranes of, cell shape and motility in relation to
.alpha.-Actinins... Actins... Myosins...
of cell membrane of sarcoma, cell shape and motility in relation to

2/7/17 (Item 17 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

82134422 CA: 82(21)134422r JOURNAL
Calcium-promoted aggregation of erythrocyte membrane proteins
AUTHOR(S): Carraway, Kermit L.; Triplett, Richard B.; Anderson, Darrell R.
LOCATION: Dep. Biochem., Oklahoma State Univ., Stillwater, Okla.
JOURNAL: Biochim. Biophys. Acta DATE: 1975 VOLUME: 379 NUMBER: 2
PAGES: 571-81 CODEN: BBACAQ LANGUAGE: English

SECTION:
CA906003 General Biochemistry
IDENTIFIERS: protein aggregation calcium membrane, erythrocyte protein aggregation calcium
DESCRIPTORS:
Proteins...
aggregation of, of erythrocyte membrane, calcium induction of
Spectrins...
of erythrocyte membrane calcium-aggregated proteins
Hemolysis...
protein of erythrocyte membrane aggregation during, in calcium presence
Erythrocyte...
proteins of membranes of, calcium-induced aggregation of
CAS REGISTRY NUMBERS:
7440-70-2 properties, aggregation of protein of erythrocyte membrane induction by
? s (b7 or b7(w)1) and (7b6 or 16c10 or 7c10 or 20c9)

Processing
8677 B7
8677 B7
9423137 1
2267 B7(W)1
33 7B6
0 16C10
16 7C10
12 20C9
S3 7 (B7 OR B7(W)1) AND (7B6 OR 16C10 OR 7C10 OR 20C9)
? rd s3

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
S4 3 RD S3 (unique items)
? t s4/7/all

4/7/1 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10923287 BIOSIS Number: 97123287
Induction of B cell costimulatory function by recombinant murine CD40 ligand
Kennedy M K; Mohler K M; Shanebeck K D; Baum P R; Picha K S; Otten-Evans C A; Janeway C A Jr; Grabstein K H
Dep. Immunobiol., Immunex Res. Dev. Corp., 51 University St., Seattle, WA 98101, USA
European Journal of Immunology 24 (1). 1994. 116-123.
Full Journal Title: European Journal of Immunology
ISSN: 0014-2980
Language: ENGLISH
Print Number: Biological Abstracts Vol. 097 Iss. 006 Ref. 073162
T cell-dependent regulation of B cell growth and differentiation involves an interaction between CD40, a B cell surface molecule, and the CD40 ligand (CD40L) which is expressed on activated CD4+ T cells. In the current study, we show that recombinant membrane-bound murine CD40L induces B cells to express costimulatory function for the proliferation of CD4+ T cells. CD40L- or lipopolysaccharide (LPS)-activated, but not control-cultured B cells were strong costimulators of anti-CD3 or alloantigen-dependent T-cell responses. The molecular interactions responsible for the increased costimulatory functions were examined by analyzing the activated B cells for changes in the expression of two costimulatory molecules, **B7** and heat-stable antigen (HSA), as well as by the use of antagonists of **B7**

and HSA (CTLA4.Fc and **20C9**, respectively). The expression of both **B7** and HSA was enhanced on B cells activated with LPS. As observed in previous studies, the costimulatory activity of the LPS-activated B cells was dependent on both **B7** and HSA and was completely inhibited in the presence of a combination of CTLA4.Fc and **20C9** . In contrast, activation of B cells with CD40L induced the expression of **B7** but did not enhance the expression of HSA. In addition the costimulatory activity of the CD40L-activated B cells was partially, but not completely, inhibited by the combination of CTLA4.Fc and **20C9**. These results demonstrate that CD40L regulates costimulatory function of B cells in part by inducing the expression of **B7** and suggest that CD40L-activated B cells express an additional costimulatory activity that is not associated with LPS-activated B cells.

4/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

10028274 BIOSIS Number: 95028274
CO-STIMULATION OF MURINE CD4 T CELL GROWTH COOPERATION BETWEEN **B7** AND HEAT-STABLE ANTIGEN
LIU Y; JONES B; BRADY W; JANEWAY C A JR; LINLEY P S
DIV. IMMUNOL., DEP. PATHOL., NEW YORK UNIV. MED. CENT., 550 FIRST AVE., NEW YORK, N.Y. 10016, USA.
EUR J IMMUNOL 22 (11). 1992. 2855-2860. CODEN: EJIMA
Full Journal Title: European Journal of Immunology
Language: ENGLISH
The B cell activation antigen **B7**/BB1 has been shown to co-stimulate growth of human T cells by binding the T cell molecule CD28. In mice, the heaert-stable antigen (HSA) has also been shown to act as a co-stimulator for T cell growth. In this study, we have evaluated the contributions of **B7** and HSA to the co-stimulatory activity of antigen-presenting cells (APC). Mouse **B7** provides co-stimulatory activity for murine CD4 T cells in anti-CD3-induced proliferation. Human CTLA4Ig, a chimeric molecule comprising the extracellular region of CTLA-4 fused to an immunoglobulin C.gamma. fragment, binds to murine **B7** . We, therefore, use human CTLA4Ig and the hamster anti-HSA monoclonal antibody **20C9** to analyze the relative contributions of **B7** and HSA to the co-stimulatory activity of murine spleen APC. Our data reveal that both murine **B7** and HSA are expressed by dendritic cells and by low-density spleen B cells. Either CTLA4Ig alone or anti-HSA alone inhibited CD4 T cell proliferation to anti-CD3 by > 90%, while CTLA4Ig and anti-HSA together were far more efficient in inhibiting clonal expansion of CD4 T cells. These results demonstrate that functionally defined co-stimulation involves at least **B7** and HSA and suggest that signals delivered by **B7** and HSA synergize in promoting T cell growth.

4/7/3 (Item 1 from file: 351)
DIALOG(R)File 351:DERWENT WPI

011869691 **Image available**
WPI Acc No: 98-286601/199825
New monoclonal antibodies specific for **B7.1** or **B7**.2 antigens and inhibiting binding to CD28 - useful as specific immunosuppressants for treating diseases that involve interactions between T and B cells, e.g. graft rejection or tumours
Patent Assignee: IDEC PHARM CORP (IDEC-N)
Inventor: ANDERSON D R; BRAMS P; HANNA N
Number of Countries: 078 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Main IPC	Week
WO 9819706	A1	19980514	WO 97US19906	A	19971029	A61K-039/395	199825 B

Priority Applications (No Type Date): US 96746361 A 19961108
Patent Details:

Patent	Kind	Lan	Pg	Filing Notes	Application	Patent
WO 9819706	A1	E	86			

Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
Designated States (Regional): AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW

Abstract (Basic): WO 9819706 A

New monoclonal antibody (MAb) that binds selectively to **B7**.**1** (CD80) or to **B7**.2 (CD86) antigens and inhibits binding of these antigens to CD28, is new. Also new are monoclonal antibodies that: (a) bind to the same epitope as MAb16D10 or **7C10**, and (b) inhibit binding of these antibodies to **B7**.**1**.

USE - MAb are specific immunosuppressants for treatment of diseases involving T cell/B cell interactions, particularly: (a) autoimmune disease, specifically idiopathic thrombocytopaenia purpura, systemic lupus erythematosus, type I diabetes mellitus, rheumatoid arthritis, psoriasis, aplastic anaemia, inflammatory bowel disease, allergy and multiple sclerosis (many others disclosed); (b) graft vs. host disease; (c) B cell lymphoma, infections (including by human immune deficiency virus) or inflammatory disease (all claimed), and (d) tumours. Optionally MAb are conjugated to a drug or toxin. MAb, or their fragments, can also be used as imaging agents and as vaccines or immunogens to develop anti-idiotype reagents. MAb are optionally combined with other proteins or small molecule immunosuppressants. The usual dose is 0.05-100 (especially 0.5-10) mg/kg/day, given orally, parenterally, by inhalation or topically.

ADVANTAGE - Blocking **B7**/CD28 interactions induces long-term, antigen-specific immunosuppression, i.e. it inhibits production of interleukin-2 (IL-2), T cell proliferation and antigen-specific immunoglobulin G (IgG) responses.

Dwg.1/10

Derwent Class: B04; D16
International Patent Class (Main): A61K-039/395
International Patent Class (Additional): C07K-016/18; C07K-016/28

s

Set Items Description
S1 17 E1,E5,E6
S2 17 RD S1 (unique items)
S3 7 (B7 OR B7(W)1) AND (7B6 OR 16C10 OR 7C10 OR 20C9)
S4 3 RD S3 (unique items)
? s (b7 or b7(w)1) and 133 and antibod?

Processing
8677 B7
8677 B7
9423137 1
2267 B7(W)1
27705 133
1052581 ANTIBOD?
S5 6 (B7 OR B7(W)1) AND 133 AND ANTIBOD?
? rd s5

>>>Duplicate detection is not supported for File 351.

>>>Records from unsupported files will be retained in the RD set.
...completed examining records
S6 3 RD S5 (unique items)
? t s6/7/all

6/7/1 (Item 1 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

13762032 BIOSIS Number: 99762032
Murine CTLA4-IgG treatment inhibits airway eosinophilia and hyperresponsiveness and attenuates IgE upregulation in a murine model of allergic asthma
Van Oosterhout A J M; Hofstra C L; Shields R; Chan B; Van Ark I; Jardieu P M; Nijkammp F P
Dep. Pharmacol. Pathophysiol., Utrecht Inst. Pharm. Sci., Utrecht Univ., P.O. Box 80.082, 3508 TB Utrecht, Netherlands
American Journal of Respiratory Cell and Molecular Biology 17 (3). 1997. 386-392.
Full Journal Title: American Journal of Respiratory Cell and Molecular Biology
ISSN: 1044-1549
Language: ENGLISH
Print Number: Biological Abstracts Vol. 104 Iss. 009 Ref. 136813
Antigen-specific T-cell activation requires the engagement of the T-cell receptor (TCR) with antigen as well as the engagement of appropriate costimulatory molecules. One of the most important pathways of costimulation is the interaction of CD28 on the T cell with **B7-1/B7** -2 on antigen-presenting cells. In the present study, we have examined the in vivo effects of blocking the CD28:**B7** T-cell costimulatory pathway by administration of mCTLA4-IgG in a murine model of allergic asthma. Mice were sensitized with ovalbumin and exposed to repeated ovalbumin inhalation challenges. In mice treated with a control **antibody** at the time of ovalbumin challenge a significant increase in the number of eosinophils (12.8 +- 4.3 times 103 cells, P lt 0.05) in the bronchoalveolar lavage (BAL) fluid and airway hyperresponsiveness to

methacholine (49 +- 15%, P lt 0.05) was observed. In addition, serum levels of ovalbumin-specific IgE were significantly (P lt 0.01) increased after ovalbumin challenge compared with saline challenge (1, **133** +- 261 experimental units (EU)/ml and 220 +- 63 EU/ml, respectively). In mice treated with mCTLA4-IgG at the time of ovalbumin challenge, the infiltration of eosinophils into BAL fluid and the development of airway hyperresponsiveness to methacholine were completely inhibited. The upregulation of ovalbumin-specific IgE levels in serum was attenuated by mCTLA4-IgG treatment. Furthermore, addition of mCTLA4-IgG to cultures of parabronchial lymph node cells from sensitized mice inhibited the ovalbumin-induced interleukin-4 production. These data indicate the therapeutic potential of blocking T-lymphocyte costimulation by CTLA4-IgG as a possible immunosuppressive treatment for patients with allergic asthma.

6/7/2 (Item 2 from file: 55)
DIALOG(R)File 55:BIOSIS PREVIEWS(R)

9019756 BIOSIS Number: 93004756
MAJOR HISTOCOMPATIBILITY COMPLEX MHC COMPLEMENT DEFICIENCY ANCESTRAL HAPLOTYPES AND SYSTEMIC LUPUS ERYTHEMATOSUS SLE C4 DEFICIENCY EXPLAINS SOME BUT NOT ALL OF THE INFLUENCE OF THE MHC
CHRISTIANSEN F T; ZHANG W J; GRIFFITHS M; MALLAL S A; DAWKINS R L
DEP. CLIN. IMMUNOL., ROYAL PERTH HOSP., GPO BOX X2213, PERTH, WESTERN AUST. 6001.
J RHEUMATOL 18 (9). 1991. 1350-1358. CODEN: JRHUA
Full Journal Title: Journal of Rheumatology
Language: ENGLISH
In 1982 we reported that among Caucasians with systemic lupus erythematosus (SLE) there is an increased frequency of C4A null. As this allele occurs on the HLA-A1,B8,BfS,C4AQO,B1,DR3 (8.1) supratype, we suggested this accounted for the reported association of B8 and DR3. Since then we have shown that many supratypes including 8.1 identify unique segments of DNA conserved from a common but remote ancestor. Many of these ancestral haplotypes (AH), including 8.1, carry disease genes and some bear C4 null. We have therefore tested the hypothesis that in SLE C4 null alleles are directly involved by examining (1) whether all or only some AH bearing C4 null alleles are increased, (2) whether C4 null is increased in all racial groups examined, and (3) whether C4 null is associated with the presence of antinuclear **antibodies** (ANA) in the absence of SLE. We performed HLA and complement allotyping on 62 Australian Caucasians and 9 Australian aborigines with SLE and on the 10 out of **133** healthy individuals with 7 or more international units of ANA. Our data confirm an association of C4A null in Australian Caucasians (gene frequency 0.30 versus 0.15 in controls) and show an increased frequency of C4B null in Australian aborigines (gene frequency 0.33 versus 0.22). A review of an extensive literature shows C4A and/or C4B null are increased in all racial groups examined. On the other hand, the HLA-A3,**B7**,BfS,C4A3,B1,DR2 (7.1) AH rather than C4 null is associated with ANA in health. Our data indicate that while C4 nulls contribute to MHC susceptibility, other genes are likely to be involved.

6/7/3 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

5769536 EMBASE No: 85015046
HLA antigens and toxicity to gold and penicillamine in rheumatoid arthritis
Scherak O.; Smolen J.S.; Mayr W.R.; et al.
Institut fur Rheumatologie und Fokalgeschehen, A-2500 Baden AUSTRIA
J. RHEUMATOL. (CANADA) , 1984, 11/5 (610-614)

CODEN: JRHUA
LANGUAGES: ENGLISH

One hundred sixty-eight patients with rheumatoid arthritis treated with chloroquine (n = 87), gold salts (n = **133**) and/or penicillamine (n = 77) were investigated for possible associations between HLA antigens and toxic reactions. Patients with 2 or more side effects to gold and/or pencillamine had a significantly increased frequency of antigens HLA-B8 and DR3 compared to patients with one or without adverse reactions. Proteinuria to gold or penicillamine was significantly associated with HLA-B8 (relative risk (RR) 4.2) and DR3 (RR 14.0) whereas nonnephrologic side effects to gold or penicillamine were associated with **B7** and DR2 (RR 3.5 and 2.8). Patients with skin reactions to gold had a significantly greater frequency of HLA-**B7**. We found no correlation between chloroquine side effects and any HLA antigen. The results suggest a genetic predisposition to toxic reactions to gold or penicillamine based on an immunologic dysregulation.

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? b 410

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            $0.41    0.118 DialUnits File1
     $0.41  Estimated cost File1
     $0.05  TYMNET
     $0.46  Estimated cost this search
     $0.46  Estimated total session cost   0.118 DialUnits

File 410:Chronolog(R)  1981-2000 Mar/Apr
       (c) 2000 The Dialog Corporation plc

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HILIGHT set on as ''
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     $0.00  Estimated cost File410
     $0.01  TYMNET
     $0.01  Estimated cost this search
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SYSTEM:OS  - DIALOG OneSearch
  File 652:US Patents Fulltext  1971-1979
         (c) format only 2000 The Dialog Corp.
*File 652: Reassignment data current through 12/06/1999 recordings.
Due to recent processing problems, the SORT command is not working.
  File 653:US Pat.Fulltext  1980-1989
         (c) format only 2000 The Dialog Corp.
*File 653: Reassignment data current through 12/06/1999 recordings.
Due to recent processing problems, the SORT command is not working.
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         (c) format only 2000 The Dialog Corp.
*File 654: Reassignment data current through 12/06/1999 recordings.
Due to recent processing problems, the SORT command is not working.

      Set  Items  Description
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? e au=gribben john g


Ref    Items  Index-term
E1         1  AU=GRIBBEN
E2         1  AU=GRIBBEN ANTHONY
E3         0 *AU=GRIBBEN JOHN G
E4        16  AU=GRIBBIN
E5         1  AU=GRIBBIN DOROTHEA M
E6        11  AU=GRIBBIN JOHN D
E7         1  AU=GRIBBIN JOHN DEREK
E8         2  AU=GRIBBIN MICHAEL J
E9         1  AU=GRIBBIN R
E10        1  AU=GRIBBINS
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E11        1  AU=GRIBBINS WILLIAM R
E12       35  AU=GRIBBLE

          Enter P or PAGE for more
? s (ctla4 or ctla(w)4)(10n)(antibod?)

Processing
              76  CTLA4
             161  CTLA
         2732115  4
             116  CTLA(W)4
           42407  ANTIBOD?
      S1      33  (CTLA4 OR CTLA(W)4)(10N)(ANTIBOD?)
? s s1(40n)(b7(w)1 or cd28 or b7?)

Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing
Processing
              33  S1
            6698  B7
         2985590  1
             309  B7(W)1
             429  CD28
            8883  B7?
      S2      22  S1(40N)(B7(W)1 OR CD28 OR B7?)
? t s2/3/all


 2/3/1     (Item 1 from file: 654)
DIALOG(R)File 654:US Pat.Full.
(c) format only 2000 The Dialog Corp. All rts. reserv.

             03110269
Utility
BLOCKADE OF T LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING

PATENT NO.:  6,051,227
ISSUED:      April 18, 2000 (20000418)
INVENTOR(s): Allison, James Patrick, Berkeley, CA (California), US (United
             States of America)
             Leach, Dana R., Albany, CA (California), US (United States of
             America)
             Krummel, Matthew F., Berkeley, CA (California), US (United
             States of America)
ASSIGNEE(s): The Regents of the University of California, Office of
             Technology Transfer, (A U.S. Company or Corporation), Oakland,
             CA (California), US (United States of America)
             [Assignee Code(s): 13234]
APPL. NO.:   8-760,288
FILED:       December 04, 1996 (19961204)
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CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. Ser. No. 08-646,605, filed May 8, 1996, now U.S. Pat. No. 5,811,097, which is a continuation-in-part of U.S. patent application Ser. No. 08-566,853, filed Dec. 4, 1995, now U.S. Pat. No. 5,855,887, which is a continuation-in-part of U.S. Ser. No. 08-506,666, filed Jul. 25, 1995, now abandoned.

This invention was made with government support under Contract Nos. CA 40041 and CA 09179 awarded by the National Institutes of Health. The

Government has certain rights in this invention.

FULL TEXT: 1924 lines

2/3/2 (Item 2 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03028906
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,977,318
ISSUED: November 02, 1999 (19991102)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-488,062
FILED: June 07, 1995 (19950607)

This application is a divisional application of U.S. Ser. No. 08-375,390, filed Jan. 18, 1995, now U.S. Pat. No. 5,844,095, issued Dec. 1, 1981 which was a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, now U.S. Pat. No. 5,770,297, issued Jun. 23, 1998, which was a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3295 lines

2/3/3 (Item 3 from file: 654)
DIALOG(R)File 654:US Pat.Full.

03019569
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,968,510
ISSUED: October 19, 1999 (19991019)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]

APPL. NO.: 8-725,776
FILED: October 04, 1996 (19961004)

This application is a divisional application of U.S. Ser. No. 08-465,078, filed Jun. 5, 1995, which is a divisional application of Ser No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Serial No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, now U.S. Pat. No. 5,770,197 which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3280 lines

2/3/4 (Item 4 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02991195
Utility
B7-2: A CTLA4/CD28 LIGAND

PATENT NO.: 5,942,607
ISSUED: August 24, 1999 (19990824)
INVENTOR(s): Freeman, Gordon J., Brookline, MA (Massachusettes), US (United States of America)
Nadler, Lee M., Newton, MA (Massachusettes), US (United States of America)
Gray, Gary S., Brookline, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Dana-Farber Cancer Institute, (A U.S. Company or Corporation), Boston, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 11804]
APPL. NO.: 8-101,624
FILED: July 26, 1993 (19930726)

GOVERNMENT FUNDING

This invention was made with government support under CA-40216-08 awarded by the National Institutes of Health. The U.S. government therefore has certain rights in this invention.

FULL TEXT: 2677 lines

2/3/5 (Item 5 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02963695
Utility
METHODS FOR INHIBITING AN IMMUNE RESPONSE BY BLOCKING THE GP39/CD40 AND CTLA4/CD28/B7 PATHWAYS AND COMPOSITIONS FOR USE THEREWITH

PATENT NO.: 5,916,560
ISSUED: June 29, 1999 (19990629)
INVENTOR(s): Larsen, Christian P., Atlanta, GA (Georgia), US (United States of America)
Aruffo, Alejandro A., Edmonds, WA (Washington), US (United States of America)
Hollenbaugh, Diane L., Seattle, WA (Washington), US (United States of America)
Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United

States of America)
Pearson, Thomas C., Atlanta, GA (Georgia), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Pinceton, NJ (New Jersey), US (United States of America)
Emory University, (A U.S. Company or Corporation), Atlanta, GA (Georgia), US (United States of America)
[Assignee Code(s): 12419; 22921]
APPL. NO.: 8-821,400
FILED: March 20, 1997 (19970320)

This application is based on United States provisional patent application Ser. No. 60-013,751 filed on Mar. 20, 1996.

FULL TEXT: 1161 lines

2/3/6 (Item 6 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02928359
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,885,796
ISSUED: March 23, 1999 (19990323)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-465,078
FILED: June 05, 1995 (19950605)

This application is a divisional of U.S. Ser. No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, which is a continuation-in-part of U.S. Ser. No. 723,617 filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3215 lines

2/3/7 (Item 7 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02928151
Utility
CTLA4 RECEPTOR AND USES THEREOF

PATENT NO.: 5,885,579
ISSUED: March 23, 1999 (19990323)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States

of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Briston-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America) [Assignee Code(s): 22921]
APPL. NO.: 8-889,666
FILED: July 08, 1997 (19970708)

This application is a divisional of U.S. Ser. No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, now U.S. Pat. No. 5,770,137, which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3241 lines

2/3/8 (Item 8 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02918854
Utility
MONOCLONAL ANTIBODIES SPECIFIC FOR DIFFERENT EPITOPES OF HUMAN GP39 AND METHODS FOR THEIR USE IN DIAGNOSIS AND THERAPY

PATENT NO.: 5,876,950
ISSUED: March 02, 1999 (19990302)
INVENTOR(s): Siadak, Anthony W., Seattle, WA (Washington), US (United States of America)
Hollenbaugh, Diane L., Seattle, WA (Washington), US (United States of America)
Gilliland, Lisa K., Bellevue, WA (Washington), US (United States of America)
Gordon, Marcia L., Seattle, WA (Washington), US (United States of America)
Bajorath, Jurgen, Lynnwood, WA (Washington), US (United States of America)
Aruffo, Alejandro A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), New York, NY (New York), US (United States of America) [Assignee Code(s): 22921]
APPL. NO.: 8-379,057
FILED: January 26, 1995 (19950126)
FULL TEXT: 3714 lines

2/3/9 (Item 9 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02913575
Utility
METHOD OF REDUCING AN IMMUNE RESPONSE TO A RECOMBINANT ADENOVIRUS
[Coadministering said adenovirus and an antibody directed against CD4, wherein formation of neutralizing antibodies is inhibited.]

PATENT NO.: 5,872,154
ISSUED: February 16, 1999 (19990216)
INVENTOR(s): Wilson, James M., Gladwyne, PA (Pennsylvania), US (United

States of America)
Yang, Yiping, Philadelphia, PA (Pennsylvania), US (United States of America)
Trinchieri, Giorgio, Wynnewood, PA (Pennsylvania), US (United States of America)
ASSIGNEE(s): The Trustees of the University of Pennsylvania, (A U.S. Company or Corporation), Philadelphia, PA (Pennsylvania), US (United States of America)
The Wistar Institute of Anatomy & Biology, (A U.S. Company or Corporation), Philadelphia, PA (Pennsylvania), US (United States of America)
[Assignee Code(s): 64664; 92890]
APPL. NO.: 8-394,032
FILED: February 24, 1995 (19950224)

This invention was supported by the National Institutes of Health Grant No. DK 47757-02 and AI 39412-02. The United States government has certain rights in this invention.

FULL TEXT: 905 lines

2/3/10 (Item 10 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02910164
Utility
METHODS OF BLOCKING T-CELL ACTIVATION USING ANTI-B7 MONOCLONAL ANTIBODIES
[Administering to patient antibody against B7 antigen and immunosuppressive agent in synergistic mixture; treatment of transplant rejection, graft versus host disease, rheumatoid arthritis]

PATENT NO.: 5,869,050
ISSUED: February 09, 1999 (19990209)
INVENTOR(s): de Boer, Mark, Almere, NL (Netherlands)
Conroy, Leah B., Pacifica, CA (California), US (United States of America)
ASSIGNEE(s): Chiron Corporation, (A U.S. Company or Corporation), Emeryville, CA (California), US (United States of America)
[Assignee Code(s): 11661]
APPL. NO.: 8-15,147
FILED: February 09, 1993 (19930209)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 07-910,222, filed Jul. 9, 1992, now U.S. Pat. No. 5,397,703, the disclosure of which is hereby incorporated by reference.

FULL TEXT: 1288 lines

2/3/11 (Item 11 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02901431
Utility
TUMOR CELLS MODIFIED TO EXPRESS B7-2 WITH INCREASED IMMUNOGENICITY AND USES THEREFOR
[Isolated mammalian tumor cell transfected with an exogenous nucleic acid molecule encoding a mammalian B7-2 molecule]

PATENT NO.: 5,861,310
ISSUED: January 19, 1999 (19990119)

INVENTOR(s): Freeman, Gordon J., Brookline, MA (Massachusettes), US (United States of America)
Nadler, Lee M., Newton, MA (Massachusettes), US (United States of America)
Gray, Gary S., Brookline, MA (Massachusettes), US (United States of America)
ASSIGNEE(s): Dana-Farber Cancer Institute, (A U.S. Company or Corporation), Boston, MA (Massachusetts), US (United States of America)
[Assignee Code(s): 11804]
EXTRA INFO: Assignment transaction [Reassigned], recorded May 24, 1999 (19990524)
APPL. NO.: 8-456,104
FILED: May 30, 1995 (19950530)

RELATED APPLICATIONS

This application is a Continuation-in-part of U.S. Ser. No. 08-147,773 filed Nov. 3,, 1993 entitled "Tumor Cells Modified to Express B7-2 and B7-3 with Increased Immunogenicity and Uses Therefor"now abandoned. The contents of this application is incorporated herein by reference.

GOVERNMENT FUNDING

Work described herein was supported under grant CA-40216 awarded by the National Institutes of Health. The U.S. government therefore may have certain rights to this invention.

FULL TEXT: 2118 lines

2/3/12 (Item 12 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02895364
Utility
BLOCKADE OF LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING
[Lymphocyte activation in response to antigen]

PATENT NO.: 5,855,887
ISSUED: January 05, 1999 (19990105)
INVENTOR(s): Allison, James Patrick, Berkeley, CA (California), US (United States of America)
Leach, Dana R., Albany, CA (California), US (United States of America)
Krummel, Matthew F., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-566,853
FILED: December 04, 1995 (19951204)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08-506,666, filed Jul. 25, 1995, now abandoned.

This invention was made with government support under Contract Nos. CA 40041 and CA 09179 awarded by the National Institutes of Health. The Government has certain rights in this invention.

FULL TEXT: 1317 lines

2/3/13 (Item 13 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02890599
Utility
SOLUBLE CTLA4 MOLECULES AND USES THEREOF

PATENT NO.: 5,851,795
ISSUED: December 22, 1998 (19981222)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Kiener, Peter A., Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), New York, NY (New York), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-459,818
FILED: June 02, 1995 (19950602)

This is a division of application Ser. No. 08-375,390, filed Jan. 18, 1995, which is a continuation-in-part of U.S. Ser. 08-228,208, filed Apr. 15, 1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3260 lines

2/3/14 (Item 14 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02881963
Utility
CTLA4 IG FUSION PROTEINS

PATENT NO.: 5,844,095
ISSUED: December 01, 1998 (19981201)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Hopewell, NJ (New Jersey), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), New York, NY (New York), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-375,390
FILED: January 18, 1995 (19950118)

This application is a continuation-in-part of U.S. Ser. No. 08-069,693, filed May 28, 1993, now abandoned, which is a continuation of U.S. Ser. No. 07-723,617, filed Jun. 27, 1991, now abandoned, and this application is also a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15,

1994, which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, which is a continuation-in-part of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned, the contents of all of which are incorporated by reference into the present application.

FULL TEXT: 3204 lines

2/3/15 (Item 15 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02846287
Utility
BLOCKADE OF T LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING
[Decreasing growth of tumor cells by administering blocking agent which binds to extracellular domain of cytotoxic T-lymphocyte-associated molecule and inhibits signaling]

PATENT NO.: 5,811,097
ISSUED: September 22, 1998 (19980922)
INVENTOR(s): Allison, James Patrick, Berkeley, CA (California), US (United States of America)
Leach, Dana R., Albany, CA (California), US (United States of America)
Krummel, Matthew F., Berkeley, CA (California), US (United States of America)
ASSIGNEE(s): The Regents of the University of California, (A U.S. Company or Corporation), Oakland, CA (California), US (United States of America)
[Assignee Code(s): 13234]
APPL. NO.: 8-646,605
FILED: May 08, 1996 (19960508)

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 08-566,853, filed Dec. 4, 1995, which is a continuation-in-part of U.S. patent application Ser. No. 08-506,666, filed Jul. 25, 1995 now abandoned.

This invention was made with government support under Contract Nos. CA 40041 and CA 09179 awarded by the National Institutes of Health. The Government has certain rights in this invention.

FULL TEXT: 1738 lines

2/3/16 (Item 16 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02806273
Utility
MYPPPY VARIANTS OF CTL A4 AND USES THEREOF

PATENT NO.: 5,773,253
ISSUED: June 30, 1998 (19980630)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Peach, Robert, Edmonds, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation),

Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-505,058
FILED: July 21, 1995 (19950721)

This application is a continuation-in-part of U.S. Ser. No. 08-228,208, filed Apr. 15, 1994 which is a continuation-in-part of U.S. Ser. No. 08-008,898, filed Jan. 22, 1993, the contents of which is incorporated by reference into the present application.

FULL TEXT: 1624 lines

2/3/17 (Item 17 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02803111
Utility
METHODS FOR REGULATING THE IMMUNE RESPONSE USING B7 BINDING MOLECULES AND IL4-BINDING MOLECULES
[Inhibiting tissue transplant rejection]

PATENT NO.: 5,770,197
ISSUED: June 23, 1998 (19980623)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Renton, WA (Washington), US (United States of America)
Brady, William, Bothell, WA (Washington), US (United States of America)
Wallace, Philip M., Seattle, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), Princeton, NJ (New Jersey), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-8,898
FILED: January 22, 1993 (19930122)

This application is a continuation-in-part of U.S. Ser. No. 723,617, filed Jul. 27, 1991, the contents of which are incorporated by reference into the present application

FULL TEXT: 2076 lines

2/3/18 (Item 18 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02788393
Utility
RECOMBINANT ANTIBODIES FOR HUMAN THERAPY

PATENT NO.: 5,756,096
ISSUED: May 26, 1998 (19980526)
INVENTOR(s): Newman, Roland A., San Diego, CA (California), US (United States of America)
Hanna, Nabil, Olivenhain, CA (California), US (United States of America)
Raab, Ronald W., San Diego, CA (California), US (United States of America)
ASSIGNEE(s): IDEC Pharmaceuticals Corporation, (A U.S. Company or Corporation), San Diego, CA (California), US (United States of

America)
[Assignee Code(s): 40498]
APPL. NO.: 8-476,237
FILED: June 07, 1995 (19950607)

FIELD OF THE INVENTION

This application is a continuation-in-part of U.S. Ser. No. 08-379,072, filed Jan. 25, 1995 (U.S. Pat. No. 5,658,570), which is a continuation of U.S. Ser. No. 07-912,292 (abandoned), filed Jul. 10, 1992, which is a continuation-in-part of Newman et al., U.S. patent application Ser. No. 07-856,281, filed Mar. 23, 1992 (abandoned), which is a continuation-in-part of U.S. patent application Ser. No. 07-735,064, filed Jul. 25, 1991 (abandoned), the whole of which, including drawings, are hereby incorporated by reference. This invention relates to recombinant antibodies useful for human therapy, and to methods for production of such antibodies.

FULL TEXT: 1809 lines

2/3/19 (Item 19 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02778834
Utility
METHODS AND MATERIALS FOR THE INDUCTION OF T CELL ANERGY

PATENT NO.: 5,747,034
ISSUED: May 05, 1998 (19980505)
INVENTOR(s): de Boer, Mark, Beverwijk, NL (Netherlands)
Conroy, Leah B., Pacifica, CA (California), US (United States of America)
ASSIGNEE(s): Chiron Corporation, (A U.S. Company or Corporation), Emeryville, CA (California), US (United States of America)
[Assignee Code(s): 11661]
APPL. NO.: 8-200,716
FILED: February 18, 1994 (19940218)

This application is a continuation-in-part of U.S. application Ser. No. 08-015,147, filed Feb. 3, 1993, now pending, which is a continuation-in-part of U.S. application Ser. No. 07-910,222, filed Jul. 9, 1992, U.S. Pat. No. 5,397,703.

FULL TEXT: 2036 lines

2/3/20 (Item 20 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02672799
Utility
METHODS AND COMPOSITIONS FOR GENE THERAPY FOR THE TREATMENT OF DEFECTS IN LIPOPROTEIN METABOLISM

PATENT NO.: 5,652,224
ISSUED: July 29, 1997 (19970729)
INVENTOR(s): Wilson, James M., Gladwyne, PA (Pennsylvania), US (United States of America)
Kozarsky, Karen, Philadelphia, PA (Pennsylvania), US (United States of America)
Strauss, III, Jerome, Wyndmoor, PA (Pennsylvania), US (United States of America)
ASSIGNEE(s): The Trustees of the University of Pennsylvania, (A U.S. Company or Corporation), Philadelphia, PA (Pennsylvania), US

(United States of America)
[Assignee Code(s): 64664]
APPL. NO.: 8-393,734
FILED: February 24, 1995 (19950224)

This invention was supported by the National Institute of Health Grant Nos. DK 42193-05 and HD 29946. The United States government has rights in this invention.

FULL TEXT: 2071 lines

2/3/21 (Item 21 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02656220
Utility
EXPRESSION VECTORS ENCODING BISPECIFIC FUSION PROTEINS AND METHODS OF PRODUCING BIOLOGICALLY ACTIVE BISPECIFIC FUSION PROTEINS IN A MAMMALIAN CELL
[Single-stranded DNA]

PATENT NO.: 5,637,481
ISSUED: June 10, 1997 (19970610)
INVENTOR(s): Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Gilliland, Lisa K., Seattle, WA (Washington), US (United States of America)
Hayden, Martha S., San Diego, CA (California), US (United States of America)
Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Bajorath, Jurgen, Everett, WA (Washington), US (United States of America)
Fell, H. Perry, Redmond, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol-Myers Squibb Company, (A U.S. Company or Corporation), New York, NY (New York), US (United States of America)
[Assignee Code(s): 22921]
APPL. NO.: 8-121,054
FILED: September 13, 1993 (19930913)

This application is a continuation-in-part of U.S. Ser. No. 08-013,420, filed Feb. 1, 1993, now abandoned the contents of which is incorporated by reference into the present application.

FULL TEXT: 2166 lines

2/3/22 (Item 22 from file: 654)
DIALOG(R)File 654:US Pat.Full.

02434212
Utility
CHIMERIC CTLA4 RECEPTOR AND METHODS FOR ITS USE

PATENT NO.: 5,434,131
ISSUED: July 18, 1995 (19950718)
INVENTOR(s): Linsley, Peter S., Seattle, WA (Washington), US (United States of America)
Ledbetter, Jeffrey A., Seattle, WA (Washington), US (United States of America)
Damle, Nitin K., Renton, WA (Washington), US (United States of America)

Brady, William, Bothell, WA (Washington), US (United States of America)
ASSIGNEE(s): Bristol Myers Squibb Co, (A U.S. Company or Corporation), Seattle, WA (Washington), US (United States of America) [Assignee Code(s): 22921]
APPL. NO.: 8-67,684
FILED: May 26, 1993 (19930526)

This application is a divisional of U.S. Ser. No. 723,617, filed Jun. 27, 1991, now abandoned the contents of which are hereby incorporated by reference.

FULL TEXT: 1613 lines
? t s2/k/all

2/K/1 (Item 1 from file: 654)
DIALOG(R)File 654:(c) format only 2000 The Dialog Corp. All rts. reserv.

... in vivo growth of the tumor cell line V51Blim10 in the presence or absence of **antibodies** directed against **CTLA-4** or **CD28** . FIG. 1B is a graph illustrating the average tumor size in mice injected with 2X10...

...injected with V51Blim10 cells.

FIG. 2 is a graph showing the in vivo growth of **B7-51BLim10** tumors in the presence or absence of **antibodies** directed against **CTLA-4** or **CD28**.

FIG. 3 shows the rejection of wild-type colon carcinoma cells by mice

CORPORATE SOURCE: San Diego, CA, USA.
PATENT ASSIGNEE: IDEC-Pharm. 1996
PATENT NUMBER: WO 9640878 PATENT DATE: 961219 WPI ACCESSION NO.: 97-108638 (9710)
PRIORITY APPLIC. NO.: US 487550 APPLIC. DATE: 950607
NATIONAL APPLIC. NO.: WO 96US10053 APPLIC. DATE: 960606
LANGUAGE: English
ABSTRACT: A new monkey monoclonal **antibody** (MAb) or primatized Ab (PAb) specifically binds human **B7**.1 antigen and/or human **B7** .2 antigen, and may be depleting or non-depleting MAb **16C10**, **7C10**, **20C9** or **7B6** , or a PAb with variable region heavy and light chain domains of these MAbs. The PAb (DNA and protein sequences specified) may be expressed by a CHO cell culture transfectoma. The MAb or PAb may be used as an immunosuppressive in therapy of a disease by inhibition of **B7** -CD28 binding or inhibition of the **B7**:CD28 pathway. The disease is preferably an autoimmune disease (e.g. idiopathic thrombocytopenia purpura, systemic lupus erythematosus, type-1 diabetes mellitus, rheumatoid arthritis, psoriasis or multiple sclerosis) or graft-versus-host disease. Monkey MAbs recognize human proteins as foreign, some with high affinity to the desired human antigen, and since they are phylogenetically close to humans the resulting **antibodies** have a high degree of amino acid homology to those produced in humans. (81pp)

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SYSTEM:OS  - DIALOG OneSearch
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  File 357:Derwent Biotechnology Abs  1982-2000/Jun B1
         (c) 2000 Derwent Publ Ltd

      Set  Items  Description
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? s (7B6 or 16C10 or 20C9 or 7C10)(30n)(antibod? or hybridoma?)(40n)(B7? or
ctla?)

             37  7B6
              1  16C10
             12  20C9
             26  7C10
        1567084  ANTIBOD?
          55473  HYBRIDOMA?
          16562  B7?
           3747  CTLA?
      S1      5  (7B6 OR 16C10 OR 20C9 OR 7C10)(30N)(ANTIBOD? OR
                 HYBRIDOMA?)(40N)(B7? OR CTLA?)
? rd s1

...completed examining records
      S2      3  RD S1 (unique items)
? t s2/7/all


 2/7/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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08738923   BIOSIS NO.: 199395028274
Co-stimulation of murine CD4 T cell growth: Cooperation between B7 and
  heat-stable antigen.
AUTHOR: Liu Yang(a); Jones Bryan; Brady William; Janeway Charles A Jr;
  Linley Peter S
AUTHOR ADDRESS: (a)Div. Immunol., Dep. Pathol., New York Univ. Med. Cent.,
  550 First Ave., New York, N.Y. 10016**USA
JOURNAL: European Journal of Immunology  22 (11):p2855-2860 1992
ISSN: 0014-2980
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The B cell activation antigen B7/BB1 has been shown to
  co-stimulate growth of human T cells by binding the T cell molecule CD28.
  In mice, the heaert-stable antigen (HSA) has also been shown to act as a
  co-stimulator for T cell growth. In this study, we have evaluated the
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contributions of **B7** and HSA to the co-stimulatory activity of antigen-presenting cells (APC). Mouse **B7** provides co-stimulatory activity for murine CD4 T cells in anti-CD3-induced proliferation. Human **CTLA4Ig**, a chimeric molecule comprising the extracellular region of **CTLA**-4 fused to an immunoglobulin C-gamma fragment, binds to murine **B7**. We, therefore, use human **CTLA4Ig** and the hamster anti-HSA monoclonal **antibody 20C9** to analyze the relative contributions of **B7** and HSA to the co-stimulatory activity of murine spleen APC. Our data reveal that both murine **B7** and HSA are expressed by dendritic cells and by low-density spleen B cells. Either **CTLA4Ig** alone or anti-HSA alone inhibited CD4 T cell proliferation to anti-CD3 by gt 90%, while **CTLA4Ig** and anti-HSA together were far more efficient in inhibiting clonal expansion of CD4 T cells. These results demonstrate that functionally defined co-stimulation involves at least B7 and HSA and suggest that signals delivered by B7 and HSA synergize in promoting T cell growth.

2/7/2 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0226040 DBA Accession No.: 98-07637 PATENT
New monoclonal antibodies specific for B7.1 or B7.2 antigens and inhibiting binding to CD28 - monoclonal antibody, produced by monkey hybridoma cell culture, humanized antibody, primatized antibody and chimeric antibody, used for autoimmune disease therapy
AUTHOR: Anderson D R; Hanna N; Brams P
CORPORATE SOURCE: San Diego, CA, USA.
PATENT ASSIGNEE: Idec-Pharm. 1998
PATENT NUMBER: WO 9819706 PATENT DATE: 980514 WPI ACCESSION NO.: 98-286601 (9825)
PRIORITY APPLIC. NO.: US 746361 APPLIC. DATE: 961108
NATIONAL APPLIC. NO.: WO 97US19906 APPLIC. DATE: 971029
LANGUAGE: English
ABSTRACT: A new monoclonal **antibody** MAb binds selectively to **B7** .1 (CD80) or to **B7**.2 (CD86) antigens and inhibits binding of the antigens to CD28. Also new are MAbs that bind to the same epitope as MAb16D10 or **7C10** and inhibit binding of the MAbs to **B7**.1. A preferred MAb does not inhibit interaction of **B7**.1 or **B7**.2 with **CTLA** -4, inhibits production of interleukin-2 by T-lymphocytes and selectively inhibits interaction B- and T-lymphocytes by CD28/**B7** pathways. The MAb may be primatized or is a human, chimeric, mouse, human or humanized **antibody** . The MAbs are specific immunosuppressants for therapy of diseases involving T- and B-lymphocyte interactions, especially autoimmune disease such as idiopathic thrombocytopaenia purpura, systemic lupus erythematosus, diabetes-mellitus-1, rheumatoid arthritis, psoriasis, aplastic anemia, inflammatory bowel disease, allergy or multiple sclerosis, guest versus host disease, B-lymphocyte lymphoma or infection (including HIV virus) or inflammatory disease, or tumors (not claimed). The MAbs may be conjugated to a drug or toxin, etc. In an example, monkey heterohybridomas were generated from lymphocytes and KH6/B5 heteromyeloma cells. (86pp)

2/7/3 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0208644 DBA Accession No.: 97-03765 PATENT
Monkey monoclonal antibody binding human B7.1 or B7.2 antigen - expression in CHO cell culture transfectoma; primatized antibody engineering for use as an immunosuppressive for autoimmune disease or graft-versus-host disease therapy
AUTHOR: Anderson D R; Brams P; Hanna N; Shestowsky W S